Access DB# 96730

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Jennifer Kim Examiner #: 77469 Date: 6/17/03
Art Unit: 1617 Phone Number 30 8-2232 Serial Number: 10/052289
Mail Box and Bldg/Room Location: 2D19 Results Format Preferred (circle): PAPER, DISK E-MAIL.
2B14

If more than one search is submitted, please prioritize searches in order of need. ME

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Method of treatment of dopamine-related dysfunction

Inventors (please provide full names): Nichols et al.

Earliest Priority Filing Date: 1/16/01

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

1) Please search claims 1-12.

2) Please search claim 1 based on the active agents described in US Patent No. 5,597,832 + 5,659,037 + 5,668,141.

3) Please provide registry #'s of active agents in claim 2

4) Please search claim 1 with D1 agonist (A 86929 + SKF-82958)

Jan Delaval
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CM1 1E07 – 703-308-4498
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THX,

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NA Sequence (#)
AA Sequence (#)
Structure (#)
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Litigation
Fulltext
Patent Family
Other

Vendors and cost where applicable

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Sequence Systems
WWW/Internet
Other (specify)

PTO-1590 (8-01)

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=> d his l88-

     (FILE 'REGISTRY' ENTERED AT 14:32:16 ON 24 JUN 2003)

     FILE 'HCAPLUS' ENTERED AT 14:34:12 ON 24 JUN 2003

     FILE 'MEDLINE' ENTERED AT 14:35:13 ON 24 JUN 2003
L88          183 S L29
L89          268 S L31
L90          296 S L88,L89
                 E PARKINSON/CT
                 E E7+ALL
L91        26229 S E13+NT
L92          649 S E30+NT
L93           48 S L90 AND L91,L92
L94           44 S L93 AND PY<=2000
                 E ANTIPARKINSON/CT
L95           18 S E4 AND L90
L96           44 S L94 AND PY<=2000
L97           44 S L94,L96

=> fil medline
FILE 'MEDLINE' ENTERED AT 14:38:22 ON 24 JUN 2003

 FILE LAST UPDATED: 21 JUN 2003 (20030621/UP). FILE COVERS 1958 TO DATE.

 On April 13, 2003, MEDLINE was reloaded. See HELP RLOAD for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2003 vocabulary. See http://www.nlm.nih.gov/mesh/changes2003.html
 for a description on changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d all tot l97

L97  ANSWER 1 OF 44     MEDLINE
AN   2001176941     MEDLINE
DN   21033217   PubMed ID: 11192626
TI   Dopaminergic regulation of synaptotagmin I and IV mRNAs in
     hemiparkinsonian rats.
AU   Glavan G; Zorec R; Babic K; Sket D; Zivin M
CS   Brain Research Laboratory, Institute of Pathophysiology, School of
     Medicine, University of Ljubljana, Slovenia.
SO   NEUROREPORT, (2000 Dec 18) 11 (18) 4043-7.
     Journal code: 9100935. ISSN: 0959-4965.
CY   England: United Kingdom
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   200103
ED   Entered STN: 20010404
     Last Updated on STN: 20010404
     Entered Medline: 20010329
AB   Synaptotagmins (Syts) I and IV are synaptic proteins involved in the
     regulation of neurosecretion. Dopaminergic drugs have been shown to
     modulate their expression. Here we investigate whether dopaminergic
     regulation of syt I and syt IV expression could play a role in the
     hypersensitive striatum of rats with unilateral lesions of dopaminergic
     nigrostriatal neurons with 6-hydroxydopamine. We show that chronic
     dopaminergic denervation resulted in a small down-regulation of striatal
     syt I mRNA, whereas acute treatment with SKF-82958, a
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dopamine D1 receptor agonist, induced a massive syt IV mRNA upregulation in the striatum on the lesioned side. We conclude that chronic lack of dopamine and treatment with dopamine D1 receptor agonists alter the synaptic plasticity in dopamine depleted basal ganglia.

CT Check Tags: Animal; Male; Support, Non-U.S. Gov't
Benzazepines: PD, pharmacology
Denervation: AE, adverse effects
*Dopamine: DF, deficiency
Dopamine Agonists: PD, pharmacology
Down-Regulation: DE, drug effects
Down-Regulation: PH, physiology
*Membrane Glycoproteins: GE, genetics
Neostriatum: DE, drug effects
*Neostriatum: ME, metabolism
Neostriatum: PP, physiopathology
*Nerve Tissue Proteins: GE, genetics
Neuronal Plasticity: DE, drug effects
Neuronal Plasticity: PH, physiology
Oxidopamine: AE, adverse effects
Parkinsonian Disorders: GE, genetics
***Parkinsonian Disorders: ME, metabolism**
Parkinsonian Disorders: PP, physiopathology
RNA, Messenger: DE, drug effects
RNA, Messenger: ME, metabolism
Rats
Rats, Wistar
Receptors, Dopamine D1: DE, drug effects
Receptors, Dopamine D1: ME, metabolism

RN 1199-18-4 (Oxidopamine); 134193-27-4 (synaptotagmin); 51-61-6 (Dopamine); **80751-65-1 (SK&F 82958)**

CN 0 (Benzazepines); 0 (Dopamine Agonists); 0 (Membrane Glycoproteins); 0 (Nerve Tissue Proteins); 0 (RNA, Messenger); 0 (Receptors, Dopamine D1)

L97 ANSWER 2 OF 44 MEDLINE
AN 2000420427 MEDLINE
DN 20336629 PubMed ID: 10877836
TI Enhanced levels of endogenous cannabinoids in the globus pallidus are associated with a reduction in movement in an animal model of Parkinson's disease.
AU Di Marzo V; Hill M P; Bisogno T; Crossman A R; Brotchie J M
CS School of Biological Sciences, University of Manchester, United Kingdom.. vdimarzo@icmib.na.cnr.it
SO FASEB JOURNAL, **(2000 Jul)** 14 (10) 1432-8.
Journal code: 8804484. ISSN: 0892-6638.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200009
ED Entered STN: 20000915
Last Updated on STN: 20000915
Entered Medline: 20000905
AB In recent years, cannabinoid receptors and their endogenous ligands (endocannabinoids) have been identified within the brain. The high density of CB1 cannabinoid receptors within the basal ganglia suggests a potential role for endocannabinoids in the control of voluntary movement and in basal ganglia-related movement disorders such as Parkinson's disease. However, whether endocannabinoids play a role in regulating motor behavior in health and disease is unknown. Here we report the presence in two regions of the basal ganglia, the globus pallidus and substantia nigra, of the endocannabinoids 2-arachidonoylglycerol (2AG) and anandamide. The levels of the latter compound are approximately threefold higher than those previously reported in any other brain region. In the

reserpine-treated rat, an animal model of Parkinson's disease, suppression of locomotion is accompanied by a sevenfold increase in the levels of the 2AG in the globus pallidus, but not in the other five brain regions analyzed. Stimulation of locomotion in the reserpine-treated rat by either of the two selective agonists of D2 and D1 dopamine receptors, quinpirole and R-(+/-)-3-allyl-6-chloro-7, 8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide (Cl-APB), respectively, results in the reduction of both anandamide and 2AG levels in the globus pallidus. Finally, full restoration of locomotion in the reserpine-treated rat is obtained by coadministration of quinpirole and the selective antagonist of the cannabinoid CB1 receptor subtype, SR141716A. These findings indicate a link between endocannabinoid signaling in the globus pallidus and symptoms of Parkinson's disease in the reserpine-treated rat, and suggest that modulation of the endocannabinoid signaling system might prove useful in treating this or other basal ganglia-related movement disorders.

CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't
Arachidonic Acids: ME, metabolism
Benzazepines: PD, pharmacology
*Cannabinoids: ME, metabolism
Dopamine Agonists: PD, pharmacology
*Globus Pallidus: ME, metabolism
Glycerides: ME, metabolism
*Motor Activity: PH, physiology
***Parkinsonian Disorders: ME, metabolism**
***Parkinsonian Disorders: PP, physiopathology**
Piperidines: PD, pharmacology
Pyrazoles: PD, pharmacology
Quinpirole: PD, pharmacology
Rats
Rats, Sprague-Dawley
Receptors, Drug: AI, antagonists & inhibitors
Reserpine: TO, toxicity
Substantia Nigra: ME, metabolism
Tissue Distribution

RN 158681-13-1 (SR 141716A); 50-55-5 (Reserpine); 53847-30-6 (2-arachidonylglycerol); **80751-65-1 (SK&F 82958)**; 85760-74-3 (Quinpirole); 94421-68-8 (anandamide)

CN 0 (Arachidonic Acids); 0 (Benzazepines); 0 (Cannabinoids); 0 (Dopamine Agonists); 0 (Glycerides); 0 (Piperidines); 0 (Pyrazoles); 0 (Receptors, Drug); 0 (cannabinoid receptor)

L97 ANSWER 3 OF 44 MEDLINE
AN 2000386500 MEDLINE
DN 20315902 PubMed ID: 10856448
TI 5-HT(2C) receptor antagonists enhance the behavioural response to dopamine D(1) receptor agonists in the 6-hydroxydopamine-lesioned rat.
AU Fox S H; Brotchie J M
CS School of Biological Sciences, Division of Neuroscience, Manchester Movement Disorder Laboratory, University of Manchester, Room 1.124, Oxford Road, M13 9PT, Manchester, UK.
SO EUROPEAN JOURNAL OF PHARMACOLOGY, **(2000 Jun 9)** 398 (1) 59-64. Journal code: 1254354. ISSN: 0014-2999.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200008
ED Entered STN: 20000818
Last Updated on STN: 20000818
Entered Medline: 20000810
AB Non-dopaminergic therapies are of potential interest in the treatment of Parkinson's disease given the complications associated with current dopamine-replacement therapies. In this study we demonstrate that SB

206553 (5-methyl-1-(3-pyridylcarbamoyl)-1,2,3, 5-tetrahydropyrrol[2,3-f]indole) (20 mg/kg) enhanced the actions of the dopamine D(1) receptor agonist, **SKF 82958** ((+)-6-chloro-7, 8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide) (1 mg/kg), in eliciting locomotion in the 6-hydroxydopamine-lesioned rat model of Parkinson's disease. This action was only seen following prior priming with L-DOPA (L-3, 4-dihydroxyphenylalanine). SB 206553 had no effect on rotational behaviour when given alone. 5-HT(2C) receptor antagonists may have potential as a means of reducing reliance on dopamine replacement in the treatment of Parkinson's disease.

CT Check Tags: Animal; Male; Support, Non-U.S. Gov't
Antiparkinson Agents: PD, pharmacology
*Behavior, Animal: DE, drug effects
Benzazepines: PD, pharmacology
Disease Models, Animal
Dopamine Agonists: PD, pharmacology
Indoles: PD, pharmacology
Levodopa: PD, pharmacology
Locomotion: DE, drug effects
Oxidopamine: AE, adverse effects
Parkinson Disease, Secondary: CI, chemically induced
Parkinson Disease, Secondary: DT, drug therapy
Parkinson Disease, Secondary: PP, physiopathology
Pyridines: PD, pharmacology
Rats
Rats, Sprague-Dawley
*Receptors, Dopamine D1: AG, agonists
*Receptors, Serotonin: DE, drug effects
*Serotonin Antagonists: PD, pharmacology

RN 1199-18-4 (Oxidopamine); **80751-65-1 (SK&F 82958)**

CN 0 (Antiparkinson Agents); 0 (Benzazepines); 0 (Dopamine Agonists); 0 (Indoles); 0 (Levodopa); 0 (Pyridines); 0 (Receptors, Dopamine D1); 0 (Receptors, Serotonin); 0 (SB 206553); 0 (Serotonin Antagonists); 0 (serotonin 2C receptor)

L97 ANSWER 4 OF 44 MEDLINE

AN 2000304943 MEDLINE

DN 20304943 PubMed ID: 10844038

TI Long-term rAAV-mediated gene transfer of GDNF in the rat Parkinson's model: intrastriatal but not intranigral transduction promotes functional regeneration in the lesioned nigrostriatal system.

AU Kirik D; Rosenblad C; Bjorklund A; Mandel R J

CS Wallenberg Neuroscience Center, Department of Physiological Sciences, Division of Neurobiology, Lund University, 223 62 Lund, Sweden.. deniz.kirik@mphy.lu.se

SO JOURNAL OF NEUROSCIENCE, **(2000 Jun 15)** 20 (12) 4686-700. Journal code: 8102140. ISSN: 0270-6474.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200006

ED Entered STN: 20000714
Last Updated on STN: 20000714
Entered Medline: 20000630

AB Previous studies have used recombinant adeno-associated viral (rAAV) vectors to deliver glial cell line-derived neurotrophic factor (GDNF) in the substantia nigra to protect the nigral dopamine (DA) neurons from 6-hydroxydopamine-induced damage. However, no regeneration or functional recovery was observed in these experiments. Here, we have used an rAAV-GDNF vector to express GDNF long-term (6 months) in either the nigral DA neurons themselves, in the striatal target cells, or in both of these

structures. The results demonstrate that both nigral and striatal transduction provide significant protection of nigral DA neurons against the toxin-induced degeneration. However, only the rats receiving rAAV-GDNF in the striatum displayed behavioral recovery, accompanied by significant reinnervation of the lesioned striatum, which developed gradually over the first 4-5 months after the lesion. GDNF transgene expression was maintained at high levels throughout this period. These results provide evidence that rAAV is a highly efficient vector system for long-term expression of therapeutic proteins in the nigrostriatal system.

CT Check Tags: Animal; Female; Support, Non-U.S. Gov't
Benzazepines: PD, pharmacology
Corpus Striatum: DE, drug effects
*Corpus Striatum: PP, physiopathology
Dependovirus
Dopamine Agonists: PD, pharmacology
*Gene Therapy
*Gene Transfer Techniques
Genes, Reporter
Genetic Vectors
Luminescent Proteins: AN, analysis
Luminescent Proteins: GE, genetics
*Nerve Regeneration: PH, physiology
*Nerve Tissue Proteins: GE, genetics
Nerve Tissue Proteins: PH, physiology
*Neuroprotective Agents
Oxidopamine: TO, toxicity
Parkinsonian Disorders: PP, physiopathology
***Parkinsonian Disorders: TH, therapy**
Rats
Rats, Sprague-Dawley
Signal Transduction
Substantia Nigra: DE, drug effects
*Substantia Nigra: PP, physiopathology
Tyrosine 3-Monooxygenase: AN, analysis

RN 1199-18-4 (Oxidopamine); 147336-22-9 (green fluorescent protein); **80751-65-1 (SK&F 82958)**

CN 0 (Benzazepines); 0 (Dopamine Agonists); 0 (Genetic Vectors); 0 (Luminescent Proteins); 0 (Nerve Tissue Proteins); 0 (Neuroprotective Agents); 0 (glial cell-line derived neurotrophic factor); EC 1.14.16.2 (Tyrosine 3-Monooxygenase)

L97 ANSWER 5 OF 44 MEDLINE
AN 2000249089 MEDLINE
DN 20249089 PubMed ID: 10785458
TI 125I-CGP 64213 binding to GABA(B) receptors in the brain of monkeys: effect of MPTP and dopaminomimetic treatments.
AU Calon F; Morissette M; Goulet M; Grondin R; Blanchet P J; Bedard P J; Di Paolo T
CS Oncology and Molecular Endocrinology Research Center, Laval University Medical Center (CHUL), Quebec, Qc, G1V 4G2, Canada.
SO EXPERIMENTAL NEUROLOGY, **(2000 May)** 163 (1) 191-9.
Journal code: 0370712. ISSN: 0014-4886.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200006
ED Entered STN: 20000622
Last Updated on STN: 20000622
Entered Medline: 20000613
AB Much evidence indicates that abnormal GABA neurotransmission may be implicated in the pathophysiology of Parkinson's disease (PD) and dopaminomimetic-induced dyskinesias (DID). In this study, autoradiography

using (125)I-CGP 64213 was performed to investigate GABA(B) receptor density in the brain of control monkeys as well as monkeys with MPTP-induced nigrostriatal depletion. Three MPTP monkeys received pulsatile administrations of the D1 dopamine (DA) receptor agonist (**SKF 82958**) whereas a long-acting D2 DA receptor agonist (cabergoline) was given to another three animals. **SKF 82958** treatment relieved parkinsonian symptoms but two of three animals developed DID. Cabergoline induced a comparable motor benefit effect without persistent DID. (125)I-CGP 64213 binding to GABA(B) receptors was heterogeneous throughout the brain with the highest levels in the medial habenula of the thalamus. MPTP induced a decrease (-40%) of (125)I-CGP 64213 binding to GABA(B) receptors in the substantia nigra pars compacta (SNpc) and an increase (+29%) in the internal segment of the globus pallidus (GPi). This increase in the GPi was not affected by **SKF 82958** but partly reversed by cabergoline. No change was seen in the striatum, the thalamus, the external segment of the globus pallidus, and the substantia nigra pars reticulata following MPTP and dopaminomimetic treatments. The changes of GABA(B) receptors observed in the SNpc and in the GPi suggest that alteration of GABA(B) receptors may play a role in the pathophysiology of PD and DID.

CT Check Tags: Animal; Female; Support, Non-U.S. Gov't
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
Antiparkinson Agents: PD, pharmacology
Autoradiography
Basal Ganglia: DE, drug effects
Basal Ganglia: ME, metabolism
Basal Ganglia: PA, pathology
Benzazepines: PD, pharmacology
*Benzoates: ME, metabolism
Binding Sites
Brain: DE, drug effects
*Brain: ME, metabolism
Brain: PA, pathology
Corpus Striatum: DE, drug effects
Dopamine Agonists: PD, pharmacology
Drug Administration Schedule
Dyskinesia, Drug-Induced: ME, metabolism
Ergolines: PD, pharmacology
*GABA Antagonists: ME, metabolism
Injections, Subcutaneous
Iodine Radioisotopes
Macaca fascicularis
*Organophosphorus Compounds: ME, metabolism
Parkinson Disease, Secondary: CI, chemically induced
Parkinson Disease, Secondary: DT, drug therapy
***Parkinson Disease, Secondary: ME, metabolism**
Receptors, GABA-B: AI, antagonists & inhibitors
*Receptors, GABA-B: ME, metabolism
Substantia Nigra: DE, drug effects
Substantia Nigra: PA, pathology
Thalamus: DE, drug effects
Thalamus: ME, metabolism
Thalamus: PA, pathology

RN 28289-54-5 (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine); **80751-65-1 (SK&F 82958)**; 81409-90-7 (cabergoline)

CN 0 (Antiparkinson Agents); 0 (Benzazepines); 0 (Benzoates); 0 (CGP 64213); 0 (Dopamine Agonists); 0 (Ergolines); 0 (GABA Antagonists); 0 (Iodine Radioisotopes); 0 (Organophosphorus Compounds); 0 (Receptors, GABA-B)

L97 ANSWER 6 OF 44 MEDLINE
AN 2000241742 MEDLINE
DN 20241742 PubMed ID: 10780830

TI The predictive validity of the drug-naive bilaterally MPTP-treated monkey as a model of Parkinson's disease: effects of L-DOPA and the D1 agonist **SKF 82958**.

AU Andringa G; Lubbers L; Drukarch B; Stoof J C; Cools A R
CS Research Institute of Neuroscience, Department of Neurology, Vrije Universiteit of Amsterdam, The Netherlands.

NC N01MH3003 (NIMH)
SO BEHAVIOURAL PHARMACOLOGY, **(1999 Mar)** 10 (2) 175-82.
Journal code: 9013016. ISSN: 0955-8810.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Space Life Sciences
EM 200005
ED Entered STN: 20000525
Last Updated on STN: 20000525
Entered Medline: 20000518

AB The aim of this study was twofold: (1) to study the predictive validity of the drug-naive, bilaterally MPTP-treated monkey as an animal model of Parkinson's disease (PD), and (2) to investigate the therapeutic and undesired effects of the D1 agonist **SKF 82958** as compared to L-DOPA treatment, in drug-naive and L-DOPA pretreated monkeys. A detailed ethogram was used, allowing the separation of therapeutic and undesired effects. Eight weeks after bilateral intracarotid MPTP administration, **SKF 82958** (1 mg/kg, n = 4, **SKF 82958**, naive group) or methyl-L-DOPA + carbi-dopa (10 + 2.5 mg/kg, n = 4, L-DOPA group) was administered intramuscularly for 22 days. After a drug-free period of eight weeks, the L-DOPA group was treated with **SKF 82958** for 22 days (SKF 82959, 1 mg/kg, n=4, pretreated). All drug treatments increased the parameters used classically to evaluate dopaminergic drugs, namely body displacement, dyskinesia and dystonia. However, the new detailed analysis revealed that L-DOPA, but not **SKF 82958**, had therapeutic effects, reflected by an increase in goal-directed fore-limb use. **SKF 82958**, but not L-DOPA, induced additional undesired effects; including epileptoid behaviours in both drug-naive and drug-pretreated monkeys. In one L-DOPA-unresponsive monkey, **SKF 82958** did induce minor therapeutic effects, as well as undesired effects. Although the effects of **SKF 82958** on fore-limb movements, rotational behaviours and body displacement were comparable in the naive and pretreated group, **SKF 82958** re-initiated undesired effects in the L-DOPA pretreated group from day one. It is concluded that the bilaterally MPTP-treated monkey is an animal model with predictive validity for PD: it adequately predicts the therapeutic effects and undesired effects of L-DOPA. Furthermore, it is concluded that **SKF 82958** is less effective than L-DOPA in the treatment of PD, because it did not induce therapeutic effects, but instead elicited several undesired effects.

CT Check Tags: Animal; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
*Antiparkinson Agents: TU, therapeutic use
Arm: PH, physiology
Behavior, Animal: DE, drug effects
*Benzazepines: TU, therapeutic use
*Dopamine Agents: TO, toxicity
*Dopamine Agonists: TU, therapeutic use
Dyskinesia, Drug-Induced: DT, drug therapy
Dyskinesia, Drug-Induced: PX, psychology
Dystonia: DT, drug therapy
Dystonia: PX, psychology
Electroencephalography: DE, drug effects
Epilepsy: PX, psychology
*Levodopa: TU, therapeutic use

***MPTP Poisoning: DT, drug therapy**
***MPTP Poisoning: PX, psychology**
Macaca mulatta
Motor Activity: DE, drug effects
Movement: DE, drug effects
***Parkinson Disease, Secondary: CI, chemically induced**
***Parkinson Disease, Secondary: DT, drug therapy**
Parkinson Disease, Secondary: PX, psychology
Predictive Value of Tests
*Receptors, Dopamine D1: AG, agonists
RN **80751-65-1 (SK&F 82958)**
CN 0 (Antiparkinson Agents); 0 (Benzazepines); 0 (Dopamine Agents); 0 (Dopamine Agonists); 0 (Levodopa); 0 (Receptors, Dopamine D1)

L97 ANSWER 7 OF 44 MEDLINE
AN 2000107218 MEDLINE
DN 20107218 PubMed ID: 10640310
TI D(1) dopamine receptor agonists are more effective in alleviating advanced than mild parkinsonism in 1-methyl-4-phenyl-1,2,3, 6-tetrahydropyridine-treated monkeys.
AU Goulet M; Madras B K
CS Harvard Medical School, New England Regional Primate Research Center, Division of Neurochemistry, Southborough, Massachusetts, USA.
NC DA00304 (NIDA)
DA09462 (NIDA)
NS30556 (NINDS)
+
SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, **(2000 Feb)** 292 (2) 714-24.
Journal code: 0376362. ISSN: 0022-3565.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200002
ED Entered STN: 20000309
Last Updated on STN: 20000309
Entered Medline: 20000222
AB Selective D(1) dopamine receptor agonists exert antiparkinsonian effects in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkey model of Parkinson's disease and in human Parkinson's disease. Motor impairment in idiopathic Parkinson's disease progresses from mild to severe, but the therapeutic potential of D(1) dopamine receptor agonists in early and advanced stages of parkinsonism is not known. To compare the effectiveness of D(1) agonists at different levels of impairment, we developed a model of mild and advanced parkinsonism in nonhuman primates and a rating scale that differentiated the two models. D(1) dopamine receptor agonists (SKF 81297, **dihydrexidine**) and D(2) dopamine receptor agonists [quinelorane, (+)-PHNO were administered to monkeys (Macaca fascicularis) displaying either mild parkinsonism (two doses of 0.6 mg/kg i.v. MPTP 1 month apart) or advanced parkinsonism (three doses of 0.6 mg/kg i.v. MPTP within 10 days). In normal monkeys (n = 3), SKF 81297 and **dihydrexidine** did not promote increased motor activity. In advanced parkinsonism (n = 4), D(1) and D(2) dopamine agonists effectively reversed the motor deficits. In contrast, the therapeutic benefits of D(1) agonists SKF 81297 and **dihydrexidine** were relatively limited in mild parkinsonism (n = 4). The D(2) agonists quinelorane and (+)-PHNO alleviated some symptoms in mild parkinsonism but also reduced balance and induced more dyskinesias than did D(1) agonists. Mild and advanced parkinsonism in nonhuman primates can be produced with fixed dosing regimens of MPTP. Based on the therapeutic efficacy and side effect profiles derived from these models, D(1) agonists are more promising for the treatment of advanced than of mild Parkinson's disease.

CT Check Tags: Animal; Comparative Study; Female; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine: TU, therapeutic use
Behavior, Animal: DE, drug effects
Benzazepines: AE, adverse effects
Benzazepines: TU, therapeutic use
*Dopamine Agents: TU, therapeutic use
Dopamine Agonists: AE, adverse effects
*Dopamine Agonists: TU, therapeutic use
Dyskinesia, Drug-Induced
Macaca fascicularis
Motor Activity: DE, drug effects
Motor Skills: DE, drug effects
Oxazines: AE, adverse effects
Oxazines: TU, therapeutic use
***Parkinsonian Disorders: DT, drug therapy**
Phenanthridines: AE, adverse effects
Phenanthridines: TU, therapeutic use
Quinolines: AE, adverse effects
Quinolines: TU, therapeutic use
*Receptors, Dopamine D1: DE, drug effects

RN **123039-93-0 (dihydrexidine)**; 28289-54-5 (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine); 71636-61-8 (SK&F 81297); 88058-88-2 (4-propyl-9-hydroxy-1,2,3,4a,5,6-hexahydronaphthoxazine); 97466-90-5 (quinelorane)

CN 0 (Benzazepines); 0 (Dopamine Agents); 0 (Dopamine Agonists); 0 (Oxazines); 0 (Phenanthridines); 0 (Quinolines); 0 (Receptors, Dopamine D1)

L97 ANSWER 8 OF 44 MEDLINE

AN 2000009759 MEDLINE

DN 20009759 PubMed ID: 10541734

TI Sub-chronic administration of the dopamine D(1) antagonist SKF 83959 in bilaterally MPTP-treated rhesus monkeys: stable therapeutic effects and wearing-off dyskinesia.

AU Andringa G; Stoof J C; Cools A R

CS Department of Psychoneuropharmacology, P.O. Box 9101, Faculty of Medical Sciences, University of Nijmegen, 6500 HB Nijmegen, The Netherlands.

NC N01MH3003 (NIMH)

SO PSYCHOPHARMACOLOGY, **(1999 Oct)** 146 (3) 328-34.
Journal code: 7608025. ISSN: 0033-3158.

CY GERMANY: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199912

ED Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991215

AB RATIONALE: SKF 83959 acts as a D(1) antagonist in vitro but has been claimed to induce anti-parkinsonian effects after acute administration in MPTP-treated marmosets. OBJECTIVE: The aim of the present study was to evaluate the therapeutic and undesired effects of sub-chronic administration of SKF 83959 in bilaterally MPTP-treated rhesus monkeys and to compare these effects with the effects of l-dopa and the dopamine agonist **SKF 82958**. METHODS: MPTP was given in the left carotid artery (2.5 mg) and 6 weeks later, the right carotid artery (1.25 mg). The monkeys (n = 4) had previously been treated chronically with l-dopa (22 days, 10 mg/kg) and **SKF 82958** (22 days, 1 mg/kg). Three months after the last administration of **SKF 82958**, SKF 83959 was given in a dose of 0.5 mg/kg from day 1 to day 15 and in a dose of 1.0 mg/kg from day 16 to day 18. RESULTS: SKF 83959 increased goal-directed limb movements in all animals, including

those unresponsive to l-dopa. This therapeutic effect did not diminish during treatment. With respect to body displacement and undesired effects, a large variation in the response to SKF 83959 was found: a large increase in body displacement co-occurred with oro-facial dyskinesia (n = 2), whereas a small increase in body displacement co-occurred with dystonia (n = 2). In contrast to the undesired effects of l-dopa, the dyskinetic effects of SKF 83959 were primarily limited to the first treatment day. Unlike l-dopa and **SKF 82958**, SKF 83959 did not induce epileptoid behaviour. CONCLUSION: Sub-chronic administration of SKF 83959 induced both clear-cut therapeutic effects that remained stable in time, and a limited number of dyskinetic effects that wore off during the treatment. The dopamine D(1) antagonist SKF 83959 may be considered as an alternative treatment in Parkinson's disease, especially in those patients who do not respond to L-dopa.

CT Check Tags: Animal; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
*Antiparkinson Agents: TU, therapeutic use
*Dopamine Antagonists: TU, therapeutic use
*Dyskinesia, Drug-Induced: ET, etiology
Levodopa: TU, therapeutic use
Levodopa: TO, toxicity
MPTP Poisoning: DT, drug therapy
Macaca mulatta
***Parkinson Disease: DT, drug therapy**
*Receptors, Dopamine D1: AI, antagonists & inhibitors

CN 0 (Antiparkinson Agents); 0 (Dopamine Antagonists); 0 (Levodopa); 0 (Receptors, Dopamine D1)

L97 ANSWER 9 OF 44 MEDLINE
AN 1999377543 MEDLINE
DN 99377543 PubMed ID: 10448434
TI Spontaneous blink rates correlate with dopamine levels in the caudate nucleus of MPTP-treated monkeys.
AU Taylor J R; Elsworth J D; Lawrence M S; Sladek J R Jr; Roth R H; Redmond D E Jr
CS Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut 06520, USA.
NC NS24032 (NINDS)
RSA-KO5-MH00643 (NIMH)
SO EXPERIMENTAL NEUROLOGY, **(1999 Jul)** 158 (1) 214-20.
Journal code: 0370712. ISSN: 0014-4886.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199909
ED Entered STN: 19990921
Last Updated on STN: 20000303
Entered Medline: 19990909

AB Previous studies have suggested a dopaminergic regulation of eye blink rates in human and nonhuman primates. Blockade of either dopamine (DA) D1 or DA D2 receptors or DA depletion induced by the dopaminergic neurotoxin MPTP both decrease spontaneous eye blink rates in monkeys. MPTP-induced decreases in blink rates can be reversed by administration of the full efficacy D1 agonist **dihydrexidine**, which has also been found to have dramatic antiparkinsonian effects in MPTP-treated animals. Increases in blink rates can also be induced by D1 and D2 agonists in normal animals. In the current study, we have investigated whether blink rates correlate with concentrations of DA or HVA and/or HVA:DA ratios in specific brain regions in MPTP-treated monkeys. Furthermore, the potential relationship between the severity of behavioral indices of parkinsonism and blink rates were examined. We found that (1) blink rates significantly correlate positively with concentration of DA and inversely

with HVA:DA ratios in the rostral portion of the ventromedial body of the caudate nucleus (CD), but not other subcortical regions, and (2) that severity of parkinsonism was inversely correlated with blink rate. These data support a dopaminergic regulation of blink rate and suggest that the ventromedial region of the body of the CD may be critically involved in regulation of blink rate.

CT Check Tags: Animal; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
*1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine: AE, adverse effects
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine: ME, metabolism
*Blinking: PH, physiology
Caudate Nucleus: CH, chemistry
*Caudate Nucleus: DE, drug effects
*Caudate Nucleus: ME, metabolism
Cercopithecus aethiops
Dopamine: AN, analysis
*Dopamine: ME, metabolism
*Dopamine Agents: AE, adverse effects
Dopamine Agents: ME, metabolism
Dopamine Agonists: PD, pharmacology
Homovanillic Acid: AN, analysis
Parkinson Disease, Secondary: CI, chemically induced
Parkinson Disease, Secondary: DI, diagnosis
Phenanthridines: PD, pharmacology
Severity of Illness Index
Tissue Culture

RN **123039-93-0 (dihydrexidine)**; 28289-54-5 (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine); 306-08-1 (Homovanillic Acid); 51-61-6 (Dopamine)

CN 0 (Dopamine Agents); 0 (Dopamine Agonists); 0 (Phenanthridines)

L97 ANSWER 10 OF 44 MEDLINE
AN 1999335087 MEDLINE
DN 99335087 PubMed ID: 10408602
TI Effects of intrasubthalamic injection of dopamine receptor agonists on subthalamic neurons in normal and 6-hydroxydopamine-lesioned rats: an electrophysiological and c-Fos study.
AU Hassani O K; Feger J
CS Laboratoire de Pharmacologie, Faculte de Pharmacie, Universite R. Descartes, Paris, France.
SO NEUROSCIENCE, **(1999)** 92 (2) 533-43.
Journal code: 7605074. ISSN: 0306-4522.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199909
ED Entered STN: 19991005
Last Updated on STN: 19991005
Entered Medline: 19990917
AB Subthalamic neuronal activity is controlled by a dopaminergic innervation, which may act via D1 and D2 dopamine receptors. This study investigates the effect of apomorphine and the selective D1 and D2 agonists, **SKF 82958** and quinpirole respectively, in normal and 6-hydroxydopamine-lesioned rats. The effect of microinjection of these drugs into the subthalamic nucleus was assessed by recording unit activity and the expression of the c-Fos-immunoreactive protein in the subthalamic nucleus. Dopaminergic agonists reduced the discharge rate and did not induce c-Fos expression in the normal rat. Apomorphine and quinpirole increased the discharge rate and induced a strong expression of c-Fos-like immunoreactive proteins, whereas **SKF 82958** induced a decrease of the discharge rate and a slight expression of c-Fos in 6-hydroxydopamine-lesioned rats. The striking contrast in the changes

obtained with apomorphine and quinpirole in normal and 6-hydroxydopamine-lesioned rats is discussed in relation to a hyperexpression of D2 dopaminergic receptors on the GABAergic terminals into the subthalamic nucleus. These results show that, in normal rats, dopamine agonists exert an inhibitory control on subthalamic neurons via D1 and D2 receptors. However, in 6-hydroxydopamine-lesioned rats, the hyperactivity of subthalamic neurons is also reduced by D1 receptor agonist but not by D2 dopamine agonists. This last result points out one aspect of the complex mechanisms underlying the physiopathology of Parkinson's disease.

CT Check Tags: Animal; Male; Support, Non-U.S. Gov't
Adrenergic Agents
Apomorphine: PD, pharmacology
Benzazepines: PD, pharmacology
*Dopamine Agonists: PD, pharmacology
Oxidopamine
Parkinson Disease
Proto-Oncogene Proteins c-fos: AN, analysis
*Proto-Oncogene Proteins c-fos: DE, drug effects
Quinpirole: PD, pharmacology
Rats
Rats, Sprague-Dawley
*Receptors, Dopamine D1: DE, drug effects
Receptors, Dopamine D1: PH, physiology
*Receptors, Dopamine D2: DE, drug effects
Receptors, Dopamine D2: PH, physiology
Substantia Nigra: CH, chemistry
*Substantia Nigra: DE, drug effects
Thalamic Nuclei: CH, chemistry
*Thalamic Nuclei: DE, drug effects

RN 1199-18-4 (Oxidopamine); 58-00-4 (Apomorphine); **80751-65-1 (SK&F 82958)**; 85760-74-3 (Quinpirole)

CN 0 (Adrenergic Agents); 0 (Benzazepines); 0 (Dopamine Agonists); 0 (Proto-Oncogene Proteins c-fos); 0 (Receptors, Dopamine D1); 0 (Receptors, Dopamine D2)

L97 ANSWER 11 OF 44 MEDLINE
AN 1999287510 MEDLINE
DN 99287510 PubMed ID: 10360765
TI ABT-431, a D1 receptor agonist prodrug, has efficacy in Parkinson's disease.
AU Rascol O; Blin O; Thalamas C; Descombes S; Soubrouillard C; Azulay P; Fabre N; Viallet F; Lafnitzegger K; Wright S; Carter J H; Nutt J G
CS Clinical Investigation Centre, Department of Pharmacology, INSERM U455, University Hospital, Toulouse, France.
SO ANNALS OF NEUROLOGY, **(1999 Jun)** 45 (6) 736-41.
Journal code: 7707449. ISSN: 0364-5134.
CY United States
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA English
FS Priority Journals
EM 199906
ED Entered STN: 19990712
Last Updated on STN: 19990712
Entered Medline: 19990624
AB Studies in animal models show a selective D1 receptor agonist with full functional efficacy compared with dopamine to have antiparkinsonian efficacy of similar magnitude to levodopa, without the same propensity for inducing dyskinesia. To date, no such agent has been tested in humans. ABT-431 is the prodrug of **A-86929**, a full, selective D1 receptor agonist. Subjects (n = 14) with levodopa-responsive

Parkinson's disease received five doses of ABT-431 (5, 10, 20, 30, and 40 mg) and one of placebo after a 12-hour levodopa holiday. Response was assessed by using the Unified Parkinson's Disease Rating Scale motor subsection. Dyskinesia was separately graded. ABT-431 showed efficacy significantly superior to placebo at doses of 10 mg and more, and of similar magnitude to that seen with levodopa. Dyskinesia was reduced in several patients after receiving ABT-431. There were no serious adverse events, the most common minor events being nausea and emesis, dizziness, and hypotension. Assuming that ABT-431 is not transformed in humans into an unknown active D2 metabolite, and remains selective for D1 receptors, it is the first dopamine D1 receptor agonist to demonstrate a full antiparkinsonian effect in patients with Parkinson's disease. These preliminary findings also suggest that it may exhibit a reduced tendency to provoke dyskinesia. The emergence of a well-tolerated D1 agonist should allow for the development of a better understanding of the relation between motor efficacy and dyskinesia in Parkinson's disease.

CT Check Tags: Female; Human; Male
Aged
Double-Blind Method
Middle Age
***Parkinson Disease: DT, drug therapy**
Prodrugs: AE, adverse effects
*Prodrugs: PD, pharmacology
Prodrugs: TU, therapeutic use
Pyridines: AE, adverse effects
*Pyridines: PD, pharmacology
Pyridines: TU, therapeutic use
Tetrahydronaphthalenes: AE, adverse effects
*Tetrahydronaphthalenes: PD, pharmacology
Tetrahydronaphthalenes: TU, therapeutic use

CN 0 (ABT 431); 0 (Prodrugs); 0 (Pyridines); 0 (Tetrahydronaphthalenes)

L97 ANSWER 12 OF 44 MEDLINE
AN 1999197212 MEDLINE
DN 99197212 PubMed ID: 10095083
TI Dopamine D-1 regulation of caudate neurotensin mRNA in the presence or absence of the nigrostriatal dopamine pathway.
AU Hanson G R; Keefe K A
CS Department of Pharmacology and Toxicology, University of Utah, 112 Skaggs Hall, Salt Lake City, UT 84112, USA.
NC DA09407 (NIDA)
K05 DA00378 (NIDA)
NS35575 (NINDS)
SO BRAIN RESEARCH. MOLECULAR BRAIN RESEARCH, **(1999 Mar 20)** 66 (1-2) 111-21.
Journal code: 8908640. ISSN: 0169-328X.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199905
ED Entered STN: 19990525
Last Updated on STN: 19990525
Entered Medline: 19990513
AB Changes in extrapyramidal dopamine (DA) function significantly alter the activity of striatal neurotensin (NT) systems. Specifically, stimulation of DA D-1 or D-2 receptors increases or decreases striatal NT tissue levels, respectively. In contrast, removal of D-2 receptor basal activity with either an antagonist or lesion of the nigrostriatal DA projection increases striatal NT content. To understand better the significance of these changes in the levels of NT peptide, we determined the effects of treatment with the selective D-1 agonist, **SKF 82958**, alone or in combination with a lesion of the nigrostriatal DA pathway, on

the levels of NT mRNA in various regions of the caudate nucleus. Removal of at least 90% of this DA pathway significantly increased NT mRNA in most, but not all, regions throughout the caudate nucleus. In contrast, four, but not one, administrations of **SKF 82958** (2 mg kg-1 dose-1) increased NT mRNA levels in principally middle, but not rostral, caudate regions. Lesioning the nigrostriatal DA pathway enhanced the effects of **SKF 82958** so that a lower, single dose (1 mg/kg) of this D-1 agonist also increased NT mRNA levels predominantly in the middle caudate sections. These findings demonstrate that DA D-1 receptors profoundly regulate the striatal expression of NT mRNA in a regionally selective fashion, which appears to be unique from that principally influenced by DA D-2 regulation.

CT Check Tags: Animal; Male; Support, U.S. Gov't, P.H.S.
Benzazepines: PD, pharmacology
*Caudate Nucleus: CH, chemistry
Caudate Nucleus: PH, physiology
Dopamine: AN, analysis
Dopamine: PH, physiology
Dopamine Agonists: PD, pharmacology
Extrapyramidal Tracts: CH, chemistry
Extrapyramidal Tracts: PH, physiology
In Situ Hybridization
*Neurotensin: GE, genetics
Nucleus Accumbens: CH, chemistry
Nucleus Accumbens: PH, physiology
Oxidopamine
Parkinson Disease: ME, metabolism
RNA, Messenger: AN, analysis
Rats
Rats, Sprague-Dawley
*Receptors, Dopamine D1: PH, physiology
Receptors, Dopamine D2: AI, antagonists & inhibitors
*Substantia Nigra: PH, physiology
Sympatholytics

RN 1199-18-4 (Oxidopamine); 39379-15-2 (Neurotensin); 51-61-6 (Dopamine); **80751-65-1 (SK&F 82958)**

CN 0 (Benzazepines); 0 (Dopamine Agonists); 0 (RNA, Messenger); 0 (Receptors, Dopamine D1); 0 (Receptors, Dopamine D2); 0 (Sympatholytics)

L97 ANSWER 13 OF 44 MEDLINE
AN 1999145670 MEDLINE
DN 99145670 PubMed ID: 9767387
TI Associative and limbic regions of monkey striatum express high levels of dopamine D3 receptors: effects of MPTP and dopamine agonist replacement therapies.
AU Morissette M; Goulet M; Grondin R; Blanchet P; Bedard P J; Di Paolo T; Levesque D
CS Unites 1d'Endocrinologie Moleculaire et de ; Facultes de 3Pharmacie et de, Quebec, Canada, G1V 4G2.
SO EUROPEAN JOURNAL OF NEUROSCIENCE, **(1998 Aug)** 10 (8) 2565-73.
Journal code: 8918110. ISSN: 0953-816X.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199905
ED Entered STN: 19990607
Last Updated on STN: 19990607
Entered Medline: 19990526
AB The role of the dopamine D3 receptor subtype in the central nervous system is still not well understood. It has a distinct and restricted distribution, mostly associated with limbic territories of the striatum

(olfactory tubercle and the shell of nucleus accumbens) in rat brain. Dopaminergic denervation induced by a 6-hydroxydopamine lesion of the nigrostriatal system in rat down-regulates the expression of the D3 receptor. In the present study, we investigated the functional neuroanatomy of the dopamine D3 receptor subtype in the monkey (Macaca fascicularis) basal ganglia. We also studied the effect of administration of the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and chronic D1-like (**SKF 82958**) or D2-like (cabergoline) agonist treatments on dopamine D3 receptor levels using receptor autoradiography. Our results clearly show that the distribution of D3 receptors in the monkey is more closely related to associative and limbic components of the striatum (caudate-putamen), as compared with its sensorimotor counterpart. Hence, D3 receptors may be more specifically involved in cognitive and motivational aspects of striatal functions, which are elaborated in prefrontal, temporal, parietal, cingulate and limbic cortices. Moreover, MPTP administration significantly decreased levels of D3 receptors and this effect was reversed or compensated by a chronic treatment with a D1-like, but not a D2-like, receptor agonist. The D3 receptor may represent an important target for adjunct or direct therapy designed to improve cognitive deficits observed in patients with Parkinson's disease, schizophrenia and other illnesses with frontal lobe cognitive disturbances.

CT Check Tags: Animal; Female; Male; Support, Non-U.S. Gov't
*1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine: PD, pharmacology
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine: TU, therapeutic use
Autoradiography
Corpus Striatum: DE, drug effects
*Corpus Striatum: ME, metabolism
*Dopamine Agents: PD, pharmacology
Dopamine Agents: TU, therapeutic use
Dopamine Agonists: PD, pharmacology
Dopamine Agonists: TU, therapeutic use
Limbic System: DE, drug effects
*Limbic System: ME, metabolism
Macaca fascicularis
Parkinson Disease: DT, drug therapy
Parkinson Disease: ME, metabolism
Rats
Rats, Sprague-Dawley
*Receptors, Dopamine D2: BI, biosynthesis

RN 28289-54-5 (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine)

CN 0 (Dopamine Agents); 0 (Dopamine Agonists); 0 (Receptors, Dopamine D2); 0 (dopamine-D3 receptor)

L97 ANSWER 14 OF 44 MEDLINE

AN 1999060779 MEDLINE

DN 99060779 PubMed ID: 9844789

TI Effects of the full dopamine D1 receptor agonist **dihydrexidine** in Parkinson's disease.

AU Blanchet P J; Fang J; Gillespie M; Sabounjian L; Locke K W; Gammans R; Mouradian M M; Chase T N

CS Experimental Therapeutics Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland 20892-1406, USA.

SO CLINICAL NEUROPHARMACOLOGY, **(1998 Nov-Dec)** 21 (6) 339-43.
Journal code: 7607910. ISSN: 0362-5664.

CY United States

DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)

LA English

FS Priority Journals

EM 199902

ED Entered STN: 19990301
Last Updated on STN: 19990301
Entered Medline: 19990212

AB The contribution of dopamine D1 receptor stimulation to the motor effects of dopaminergic drugs in patients with Parkinson's disease remains undetermined. The authors of this article studied the clinical efficacy, pharmacokinetics, and tolerability of the full D1 receptor agonist **dihydrexidine**, (+/-)-trans-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[a] phenanthridine hydrochloride in a double-blind, placebo-controlled trial in four patients with Parkinson's disease. Single intravenous doses were carefully titrated according to a fixed schedule ranging from 2 mg to the highest tolerated dose (or a maximum of 70 mg) infused over either 15 or 120 minutes. The only patient to achieve a plasma drug concentration greater than 100 ng/ml had a brief but definite motor improvement accompanied by choreic dyskinesias similar to the response to levodopa. Dose-limiting adverse effects, including flushing, hypotension, and tachycardia, were observed in all cases, especially with rapid infusions. No nausea or emesis occurred. Pharmacokinetic studies yielded a plasma half-life < 5 minutes. These preliminary data suggest that **dihydrexidine** has a marginal therapeutic window for providing an antiparkinsonian effect, although it remains uncertain how much of this effect is attributable to pure D1 receptor stimulation.

CT Check Tags: Human; Male; Support, Non-U.S. Gov't
Adult
Dopamine Agonists: AE, adverse effects
Dopamine Agonists: PK, pharmacokinetics
*Dopamine Agonists: TU, therapeutic use
Double-Blind Method
Middle Age
Motor Activity: DE, drug effects
***Parkinson Disease: DT, drug therapy**
Parkinson Disease: ME, metabolism
Phenanthridines: AE, adverse effects
Phenanthridines: PK, pharmacokinetics
*Phenanthridines: TU, therapeutic use
*Receptors, Dopamine D1: AG, agonists
Treatment Outcome

RN **123039-93-0 (dihydrexidine)**

CN 0 (Dopamine Agonists); 0 (Phenanthridines); 0 (Receptors, Dopamine D1)

L97 ANSWER 15 OF 44 MEDLINE

AN 1998369379 MEDLINE

DN 98369379 PubMed ID: 9703756

TI Dopamine D1 receptor agonists as antiparkinson drugs.

CM Comment on: Trends Pharmacol Sci. 1997 Sep;18(9):307-10

AU Mailman R B; Nichols D E

SO TRENDS IN PHARMACOLOGICAL SCIENCES, **(1998 Jul)** 19 (7) 255-6.
Journal code: 7906158. ISSN: 0165-6147.

CY ENGLAND: United Kingdom

DT Commentary
Letter

LA English

FS Priority Journals

EM 199810

ED Entered STN: 19981029
Last Updated on STN: 20000303
Entered Medline: 19981020

CT Check Tags: Animal; Human
*Antiparkinson Agents: TU, therapeutic use
*Dopamine Agonists: TU, therapeutic use
***Parkinson Disease: DT, drug therapy**
*Phenanthridines: TU, therapeutic use

*Receptors, Dopamine D1: AG, agonists
RN **123039-93-0 (dihydrexidine)**
CN 0 (Antiparkinson Agents); 0 (Dopamine Agonists); 0 (Phenanthridines); 0 (Receptors, Dopamine D1)

L97 ANSWER 16 OF 44 MEDLINE
AN 1998102641 MEDLINE
DN 98102641 PubMed ID: 9435192
TI Trihexyphenidyl interactions with the dopamine D1-selective receptor agonist **SKF-82958** and the D2-selective receptor agonist N-0923 in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced hemiparkinsonian monkeys.
AU Domino E F; Ni L
CS Department of Pharmacology, University of Michigan, Ann Arbor, USA.
SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, **(1998 Jan)** 284 (1) 307-11.
Journal code: 0376362. ISSN: 0022-3565.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199802
ED Entered STN: 19980224
Last Updated on STN: 20000303
Entered Medline: 19980211
AB The effects of the antiparkinsonian agent trihexyphenidyl, a selective M1 muscarinic cholinergic receptor antagonist, were studied in doses of 100, 320 and 1000 micrograms/kg i.m. alone. Trihexyphenidyl was then studied in combination with the selective dopamine receptor D1 agonist **SKF -82958** [(+/-)-6-chloro-7-8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro- 1H-benzazepine hydrobromide] and the selective D2 agonist N-0923 [(-)2-(N-propyl-N-2-thienylethyl)amino-5-hydroxytetralin HCl] on rotational behavior in five 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned hemiparkinsonian monkeys. Given alone, trihexyphenidyl had no effect on ipsiversive and slightly enhanced contraversive circling. Contraversive circling produced by 74.8 and 234 micrograms/kg **SKF -82958** i.m. was potentiated by increasing doses of trihexyphenidyl. On the other hand, contraversive circling produced by 10 and 32 micrograms/kg N-0923 i.m. was progressively reduced with increasing doses of trihexyphenidyl. The results obtained indicate differential actions on circling behavior between a selective M1 muscarinic cholinergic receptor antagonist and selective D1 and D2 receptor agonists in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine monkey model of hemiparkinsonism.
CT Check Tags: Animal; Female; Support, Non-U.S. Gov't
*Antiparkinson Agents: TU, therapeutic use
*Benzazepines: TU, therapeutic use
*Dopamine Agonists: TU, therapeutic use
Dose-Response Relationship, Drug
Drug Synergism
***MPTP Poisoning**
Macaca nemestrina
***Parkinson Disease, Secondary: DT, drug therapy**
*Receptors, Dopamine D1: AG, agonists
*Receptors, Dopamine D2: AG, agonists
*Tetrahydronaphthalenes: TU, therapeutic use
*Thiophenes: TU, therapeutic use
*Trihexyphenidyl: TU, therapeutic use
RN 144-11-6 (Trihexyphenidyl); **80751-65-1 (SK&F 82958)**; **92206-54-7 (N 0437)**
CN 0 (Antiparkinson Agents); 0 (Benzazepines); 0 (Dopamine Agonists); 0 (Receptors, Dopamine D1); 0 (Receptors, Dopamine D2); 0 (Tetrahydronaphthalenes); 0 (Thiophenes)

L97 ANSWER 17 OF 44 MEDLINE
AN 1998063032 MEDLINE
DN 98063032 PubMed ID: 9398468
TI The cannabinoid receptor agonist WIN 55,212-2 reduces D2, but not D1, dopamine receptor-mediated alleviation of akinesia in the reserpine-treated rat model of Parkinson's disease.
AU Maneuf Y P; Crossman A R; Brotchie J M
CS Division of Neuroscience, School of Biological Sciences, University of Manchester, United Kingdom.. ymaneuf@fs2.scg.man.ac.uk
SO EXPERIMENTAL NEUROLOGY, **(1997 Nov)** 148 (1) 265-70.
Journal code: 0370712. ISSN: 0014-4886.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199801
ED Entered STN: 19980122
Last Updated on STN: 20000303
Entered Medline: 19980107
AB The effects of the synthetic cannabinoid receptor agonist WIN 55,212-2 on dopamine receptor-mediated alleviation of akinesia were evaluated in the reserpine-treated rat model of parkinsonism. The dopamine D2 receptor agonist quinpirole (0.1 mg/kg, ip) caused a significant alleviation of the akinesia. This effect was significantly reduced by coinjection with the cannabinoid receptor agonist WIN 55,212-2 (0.1 and 0.3 mg/kg). The simultaneous administration of the cannabinoid receptor antagonist SR 141716A (3 mg/kg, ip) with quinpirole and WIN 55,212-2 blocked the effect of WIN 55,212-2 on quinpirole-induced alleviation of akinesia. The selective dopamine D1 receptor agonist chloro-APB (**SKF82958**, 0.1 mg/kg) alleviated akinesia in a significant manner. WIN 55,212-2 (0.1-1 mg/kg, ip) did not affect the antiakinetic effect of chloro-APB. Combined injection of both D1 and D2 dopamine receptor agonists (both at either 0.1 or 0.02 mg/kg) resulted in a marked synergism of the antiakinetic effect. WIN 55,212-2 (0.1-1 mg/kg) significantly reduced the antiakinetic effect of combined injections of quinpirole and chloro-APB at both 0.1 and 0.02 mg/kg. The effect of 0.3 mg/kg WIN 55,212-2 on combined D1 and D2 agonist-induced locomotion (0.02 mg/kg) was blocked by SR 141761A (3 mg/kg). Neither WIN 55,212-2 alone (0.1 and 0.3 mg/kg) nor SR 141716A (3 and 30 mg/kg) alone had an antiparkinsonian effect. These results suggest that cannabinoids may modulate neurotransmission in the pathway linking the striatum indirectly to basal ganglia outputs via the lateral globus pallidus and the subthalamic nucleus.
CT Check Tags: Animal; Male; Support, Non-U.S. Gov't
Basal Ganglia: DE, drug effects
Basal Ganglia: PP, physiopathology
Benzazepines: PD, pharmacology
*Benzazepines: TU, therapeutic use
Dopamine Agonists: PD, pharmacology
*Dopamine Agonists: TU, therapeutic use
Locomotion: DE, drug effects
Morpholines: PD, pharmacology
*Morpholines: TO, toxicity
Naphthalenes: PD, pharmacology
*Naphthalenes: TO, toxicity
*Nerve Tissue Proteins: DE, drug effects
Nerve Tissue Proteins: PH, physiology
Parkinson Disease, Secondary: CI, chemically induced
***Parkinson Disease, Secondary: DT, drug therapy**
Piperidines: PD, pharmacology
*Piperidines: TU, therapeutic use
Pyrazoles: PD, pharmacology
*Pyrazoles: TU, therapeutic use

Quinpirole: PD, pharmacology
*Quinpirole: TU, therapeutic use
Rats
Rats, Sprague-Dawley
*Receptors, Dopamine D1: DE, drug effects
Receptors, Dopamine D1: PH, physiology
*Receptors, Dopamine D2: DE, drug effects
Receptors, Dopamine D2: PH, physiology
*Receptors, Drug: AG, agonists
*Reserpine: TO, toxicity
gamma-Aminobutyric Acid: PH, physiology
RN 134959-51-6 (Win 55212-2); 158681-13-1 (SR 141716A); 50-55-5 (Reserpine); 56-12-2 (gamma-Aminobutyric Acid); **80751-65-1 (SK&F 82958)**; 85760-74-3 (Quinpirole)
CN 0 (Benzazepines); 0 (Dopamine Agonists); 0 (Morpholines); 0 (Naphthalenes); 0 (Nerve Tissue Proteins); 0 (Piperidines); 0 (Pyrazoles); 0 (Receptors, Dopamine D1); 0 (Receptors, Dopamine D2); 0 (Receptors, Drug); 0 (cannabinoid receptor)

L97 ANSWER 18 OF 44 MEDLINE
AN 97422109 MEDLINE
DN 97422109 PubMed ID: 9276196
TI Differential therapeutic effects of dopamine D1 and D2 agonists in MPTP-induced parkinsonian monkeys: clinical implications.
AU Kuno S
CS Department of Neurology, Utano National Hospital, Kyoto, Japan.. sakuno21@mbox.kyoto-inet.or.jp
SO EUROPEAN NEUROLOGY, **(1997)** 38 Suppl 1 18-22.
Journal code: 0150760. ISSN: 0014-3022.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199710
ED Entered STN: 19971024
Last Updated on STN: 20000303
Entered Medline: 19971016
AB L-DOPA, the precursor of dopamine, remains most effective in the treatment of patients with Parkinson's disease, but prolonged L-DOPA treatment often produces adverse effects, including dyskinesia and psychosis. Dopamine receptors can be divided into two major subtypes; D1 and D2. Might both subtypes of the dopamine receptor be equally relevant to amelioration of parkinsonian symptoms and responsible for the adverse side effects? To address this question, the effects of D1 or D2 receptor agonists alone and in joint administration were examined in MPTP-induced parkinsonian monkeys. The parkinsonian symptoms, such as tremor, bradykinesia and rigidity, and the adverse side effects, such as hyperactivity and aggressiveness, were evaluated independently using different behavioral criteria. The results showed that antiparkinsonian effects can be exerted either by the D1 agonist (**SKF 82958**) alone or by the D2 agonist (quinpirole) alone, whereas hyperactivity and aggressiveness manifested by dopamine agonists require coactivation of the D1 and D2 receptors. Thus, the antiparkinsonian effect can be dissociated from the adverse effect by therapeutic strategy. It is implied that imbalances in activation of the D1 and D2 receptors may provide a favorable approach for long-term treatment of parkinsonian patients with dopamine drugs.
CT Check Tags: Animal; Comparative Study
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
*Antiparkinson Agents: TU, therapeutic use
Apomorphine: TU, therapeutic use
Benzazepines: TU, therapeutic use
*Dopamine Agonists: TU, therapeutic use
Macaca fascicularis

***Parkinson Disease, Secondary: DT, drug therapy**
Parkinson Disease, Secondary: ET, etiology
*Receptors, Dopamine D1: AG, agonists
*Receptors, Dopamine D2: AG, agonists
RN 28289-54-5 (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine); 58-00-4 (Apomorphine); **80751-65-1 (SK&F 82958)**
CN 0 (Antiparkinson Agents); 0 (Benzazepines); 0 (Dopamine Agonists); 0 (Receptors, Dopamine D1); 0 (Receptors, Dopamine D2)

L97 ANSWER 19 OF 44 MEDLINE
AN 97416621 MEDLINE
DN 97416621 PubMed ID: 9270571
TI Potential therapeutic use of the selective dopamine D1 receptor agonist, **A-86929**: an acute study in parkinsonian levodopa-primed monkeys.
AU Grondin R; Bedard P J; Britton D R; Shiosaki K
CS Department of Pharmacology, Faculty of Medecine, Laval University, Canada.
SO NEUROLOGY, **(1997 Aug)** 49 (2) 421-6.
Journal code: 0401060. ISSN: 0028-3878.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199709
ED Entered STN: 19970926
Last Updated on STN: 20000303
Entered Medline: 19970917
AB The clinical utility of dopamine (DA) D1 receptor agonists in the treatment of Parkinson's disease (PD) is still unclear. The therapeutic use of selective DA D1 receptor agonists such as **SKF-82958** (6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzaze pine hydrobromide) and A-77636 ([1R, 3S] 3-[1'-admantyl]-1-aminomethyl-3,4-dihydro-5,6-dihydroxy-1H-2-benzo pyran hydrochloride) seems limited because of their duration of action, which is too short for **SKF-82958** (< 1 hr) and too long for A-77636 (> 20 hr, leading to behavioral tolerance). We therefore conducted the present acute dose-response study in four 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-exposed cynomolgus monkeys primed to exhibit levodopa-induced dyskinesias to evaluate the locomotor and dyskinetic effects on challenge with four doses (from 0.03 to 1.0 mg/kg) of **A-86929** ([-]-[5aR,11bS]-4,5,5a,6,7,11b-hexahydro-2-propyl-3-thia-5-+ ++azacyclopent-1- ena[c]phenathrene-9-10-diol), a selective and full DA D1-like receptor agonist with an intermediate duration of action. Levodopa and the DA D2-like receptor agonist, LY-171555 ([4aR-trans]-4,4a,5,6,7,8,8a,9-o-dihydro-5n-propyl-2H-pyrazo lo-3-4-quinoline hydrochloride) were also used for comparison. Acute administration of **A-86929** was as efficacious in alleviating MPTP-induced parkinsonism as levodopa and LY-171555, but was less likely to reproduce the levodopa-induced dyskinesias in these animals than with either LY-171555 or subsequent challenge of levodopa. Selective stimulation of the DA D1 receptor may provide better integration of neural inputs transmitted to the internal segment of the globus pallidus (referred to as the basal ganglia output) compared with levodopa and selective DA D2 receptor agonist. Potent DA D1 receptor agents with an intermediate duration of efficacy such as **A-86929** (approximately 4 hr at higher doses tested) are potential therapeutic tools in PD and merit further attention.
CT Check Tags: Animal; Female; Support, Non-U.S. Gov't
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
Antiparkinson Agents
Dopamine Agents
*Dopamine Agonists: TU, therapeutic use
Dyskinesia, Drug-Induced: DT, drug therapy

Dyskinesia, Drug-Induced: PP, physiopathology
Levodopa
Macaca fascicularis
Motor Activity: DE, drug effects
Parkinson Disease, Secondary: CI, chemically induced
***Parkinson Disease, Secondary: DT, drug therapy**
Parkinson Disease, Secondary: PP, physiopathology
*Quinolones: TU, therapeutic use
Quinpirole: TU, therapeutic use
*Receptors, Dopamine D1: AG, agonists
*Thiophenes: TU, therapeutic use
RN 28289-54-5 (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine); 85760-74-3 (Quinpirole)
CN 0 (**A 86929**); 0 (Antiparkinson Agents); 0 (Dopamine Agents); 0 (Dopamine Agonists); 0 (Levodopa); 0 (Quinolones); 0 (Receptors, Dopamine D1); 0 (Thiophenes)

L97 ANSWER 20 OF 44 MEDLINE
AN 97349921 MEDLINE
DN 97349921 PubMed ID: 9205801
TI Selective full dopamine D1-like (**SKF-82958**) and D2-like (N-0923) agonist combination in the MPTP monkey model of hemiparkinsonism.
AU Domino E F
CS Department of Pharmacology, University of Michigan, Ann Arbor 48109-0632, USA.
SO BRAIN RESEARCH BULLETIN, **(1997)** 43 (1) 93-5.
Journal code: 7605818. ISSN: 0361-9230.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199709
ED Entered STN: 19970916
Last Updated on STN: 20000303
Entered Medline: 19970904
AB Both **SKF-82958** and N-0923, selective full D1-like and D2-like agonists, respectively, given IM produced contraversive circling and reduced neurologic deficits in six MPTP-induced hemiparkinsonian monkeys. A small fixed dose of N-0923 (10 micrograms/kg) and increasing doses of **SKF-82958** (23.4-234 micrograms/kg) in combination were synergistic or antagonistic in this animal model. A small dose (23.4 micrograms/kg) of **SKF-82958**, in combination with N-0923, caused potentiation, an intermediate dose (74.8 micrograms/kg) in combination produced additive effects, while a very large dose (234 micrograms/kg) in combination produced antagonism. All three doses of **SKF-82958** prolonged the duration of action of a small dose (10 ng/kg) of N-0923. Selective D1-like and D2-like agonists should be studied as potential therapeutic agents alone and in combination in human idiopathic parkinsonism, especially using low and intermediate doses.
CT Check Tags: Animal; Female; Support, Non-U.S. Gov't
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
*Benzazepines: PD, pharmacology
Disease Models, Animal
*Dopamine Agonists: PD, pharmacology
Drug Evaluation, Preclinical
Drug Interactions
Macaca nemestrina
Parkinson Disease, Secondary: CI, chemically induced
***Parkinson Disease, Secondary: DT, drug therapy**
*Receptors, Dopamine D1: AG, agonists
*Receptors, Dopamine D2: AG, agonists

*Tetrahydronaphthalenes: PD, pharmacology
*Thiophenes: PD, pharmacology
RN 28289-54-5 (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine); **80751-65-1 (SK&F 82958)**; 92206-54-7 (N 0437)
CN 0 (Benzazepines); 0 (Dopamine Agonists); 0 (Receptors, Dopamine D1); 0 (Receptors, Dopamine D2); 0 (Tetrahydronaphthalenes); 0 (Thiophenes)

L97 ANSWER 21 OF 44 MEDLINE
AN 97315864 MEDLINE
DN 97315864 PubMed ID: 9171869
TI Substituted hexahydrobenzo[f]thieno[c]quinolines as dopamine D1-selective agonists: synthesis and biological evaluation in vitro and in vivo.
AU Michaelides M R; Hong Y; DiDomenico S Jr; Bayburt E K; Asin K E; Britton D R; Lin C W; Shiosaki K
CS Abbott Laboratories, Abbott Park, Illinois 60064-3500, USA.
SO JOURNAL OF MEDICINAL CHEMISTRY, **(1997 May 23)** 40 (11) 1585-99.
Journal code: 9716531. ISSN: 0022-2623.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199706
ED Entered STN: 19970716
Last Updated on STN: 20000303
Entered Medline: 19970627
AB A series of substituted 9,10-dihydroxyhexahydrobenzo[f]thieno[c]quinolines (TB[f]Q), varying with respect to the position of the thiophene relative to the benzo[f]quinoline core and the nature and position of the substituent on the thiophene, were prepared and evaluated for their affinity and selectivity for the dopamine D1-like receptor. The thieno[3,2-c]B[f]Q regioisomers bearing a small alkyl (C1-C3) substituent at the 2 position were potent (Ki < 20 nM) and selective (D2/D1 > 50) D1 agonists with close to full agonist activity (IA > 85%). The compounds were resolved and found to exhibit a high level of enantiospecificity in their interaction with the D1 receptor. Selected compounds were tested in vivo in the 6-OHDA rodent model of Parkinson's disease and for their liability to produce seizure-like activities in mice. (5aR)-trans-2-Propyl-4,5,5a,6,7, 11b-hexahydro-3-thia-5-azacyclopent-1-ena[c]phenanthrene-9,10-diol (5) emerged as the compound with the best overall in vivo profile in terms of potency (ED50 = 0.04 mumol/kg) and safety.
CT Check Tags: Animal
Adenylate Cyclase: ME, metabolism
Binding, Competitive
Cell Membrane: ME, metabolism
Corpus Striatum: ME, metabolism
*Dopamine Agonists: CS, chemical synthesis
Dopamine Antagonists: ME, metabolism
Fishes
Mice
Molecular Structure
Oxidopamine
Parkinson Disease, Secondary: CI, chemically induced
Parkinson Disease, Secondary: DT, drug therapy
*Quinolones: CS, chemical synthesis
Quinolones: ME, metabolism
Quinolones: TU, therapeutic use
*Receptors, Dopamine
Receptors, Dopamine: ME, metabolism
Retina: EN, enzymology
Sch-23390: ME, metabolism
Stereoisomerism
Structure-Activity Relationship
*Thiophenes: CS, chemical synthesis

Thiophenes: ME, metabolism
Thiophenes: TU, therapeutic use
Tritium
Yohimbine: ME, metabolism

RN 10028-17-8 (Tritium); 1199-18-4 (Oxidopamine); 146-48-5 (Yohimbine); 87075-17-0 (Sch-23390)

CN 0 (**A 86929**); 0 (Dopamine Agonists); 0 (Dopamine Antagonists); 0 (Quinolones); 0 (Receptors, Dopamine); 0 (Thiophenes); 0 (dopamine-I receptor); EC 4.6.1.1 (Adenylate Cyclase)

L97 ANSWER 22 OF 44 MEDLINE

AN 97306092 MEDLINE

DN 97306092 PubMed ID: 9163560

TI Talipexole or pramipexole combinations with chloro-APB (**SKF 82958**) in MPTP-induced hemiparkinsonian monkeys.

AU Domino E F; Ni L; Zhang H; Kohno Y; Sasa M

CS Department of Pharmacology, University of Michigan, Ann Arbor 48109-0632, USA.

SO EUROPEAN JOURNAL OF PHARMACOLOGY, **(1997 May 1)** 325 (2-3) 137-44. Journal code: 1254354. ISSN: 0014-2999.

CY Netherlands

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199708

ED Entered STN: 19970813
Last Updated on STN: 20000303
Entered Medline: 19970804

AB The effects of two predominant dopamine D2-like receptor agonists, talipexole (6-allyl-2-amino-5,6,7,8-tetrahydro-4H-thiazolo [4,5-d]-azepine dihydrochloride, B-HT 920 CL2) and pramipexole (S(-)2-amino-4,5,6,7-tetrahydro-6-propyl-aminobenzothiazole dihydrochloride, SND 919 CL2Y), were studied alone and in combination with the selective dopamine D1-like receptor agonist chloro-APB ((+/-)6-chloro-7-8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-benz azepine hydrobromide, **SKF 82958**) in five chronic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lesioned hemiparkinsonian Macaca nemestrina monkeys. Talipexole induced contraversive rotation in a dose-dependent manner up to 32 microg/kg, i.m. Talipexole was more potent than pramipexole (10 vs. 32 microg/kg, i.m.), but pramipexole was more efficacious in producing contraversive rotational behavior and significant hand movements in the afflicted limb. Larger doses of chloro-APB also produced contraversive rotation. Combinations of each dopamine D2-like receptor agonist in a median effective dose with chloro-APB (23.4 and 74.8 microg/kg, i.m.) had synergistic effects, producing either addition or potentiation, depending upon the dose used. The effects noted with these combinations were less than the effect of a large dose (100 microg/kg) of pramipexole. Talipexole, in the largest dose studied (100 microg/kg, i.m.), produced sedation which was not seen with the same dose of pramipexole. No significant extrapyramidal side effects were noted with either agent.

CT Check Tags: Animal; Female
Antiparkinson Agents: AD, administration & dosage
Antiparkinson Agents: TO, toxicity
*Azepines: AD, administration & dosage
Azepines: TO, toxicity
Basal Ganglia Diseases: CI, chemically induced
Behavior, Animal: DE, drug effects
*Benzazepines: AD, administration & dosage
Benzazepines: TO, toxicity
Dopamine Agents: TO, toxicity
*Dopamine Agonists: AD, administration & dosage
Dopamine Agonists: TO, toxicity

Drug Interactions
MPTP Poisoning
Macaca nemestrina
Parkinson Disease, Secondary: CI, chemically induced
***Parkinson Disease, Secondary: DT, drug therapy**
Sleep: DE, drug effects
*Thiazoles: AD, administration & dosage
Thiazoles: TO, toxicity
RN 104632-26-0 (pramipexol); 36085-73-1 (talipexole); **80751-65-1 (SK&F 82958)**
CN 0 (Antiparkinson Agents); 0 (Azepines); 0 (Benzazepines); 0 (Dopamine Agents); 0 (Dopamine Agonists); 0 (Thiazoles)

L97 ANSWER 23 OF 44 MEDLINE
AN 97256689 MEDLINE
DN 97256689 PubMed ID: 9103530
TI The selective dopamine D1 receptor agonist **A-86929** maintains efficacy with repeated treatment in rodent and primate models of Parkinson's disease.
AU Asin K E; Domino E F; Nikkel A; Shiosaki K
CS Abbott Laboratories, Neuroscience Research Division, Abbott Park, Illinois 60064-3500, USA.
SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, **(1997 Apr)** 281 (1) 454-9.
Journal code: 0376362. ISSN: 0022-3565.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199705
ED Entered STN: 19970514
Last Updated on STN: 19970514
Entered Medline: 19970502
AB The ability of the selective dopamine D1 receptor agonist (5aR,11bS)-4,5,5a,6,7,11b-hexahydro-2-propyl-3-thia-5-aza cyclopent-1-ena[c]-phenanthrene-9,10-diol (**A-86929**) to induce contralateral rotation after repeated administration was determined in rodent and primate models of Parkinson's disease. Testing was conducted in rats previously given unilateral 6-hydroxydopamine injections and in macaques previously given unilateral, intracarotid infusions of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Both treatments have been shown to reduce forebrain dopamine levels on the side of the infusion. Such animals rotate contralaterally after injections of direct-acting dopamine receptor agonists. Rats were administered **A-86929** (0.11 or 0.22 micromol/kg s.c.) three times daily for 10 days, with injections spaced 3 h apart, and rotation was measured across a 9-h period on various treatment days. Initially, monkeys were given various doses of **A-86929** (0.03, 0.10 or 0.30 micromol/kg i.m.), and rotation was monitored for 3 h after each dose. Significant, dose-dependent levels of contralateral rotation were achieved. Monkeys were next treated three times daily at 3-h intervals with **A-86929** (0.3 micromol/kg). Analysis of total, daily rotation scores indicated that the magnitude of the behavioral response did not change significantly across the 10-day treatment period in monkeys, although it increased in rats (0.22 micromol/kg). The first daily injection tended to elicit greater and longer-lived responses than the subsequent daily injections in both species. In monkeys, this was particularly true on the first test day and was not seen by the last test. This study suggests that a selective D1 receptor agonist, such as **A-86929**, with full intrinsic activity relative to dopamine, may be useful for the treatment of Parkinson's disease.
CT Check Tags: Animal; Male

Analysis of Variance
*Antiparkinson Agents: TU, therapeutic use
*Dopamine Agonists: TU, therapeutic use
Dose-Response Relationship, Drug
Macaca nemestrina
***Parkinson Disease: DT, drug therapy**
*Pyridines: TU, therapeutic use
Rats
Rats, Sprague-Dawley
*Receptors, Dopamine D1: AG, agonists
Rotation
*Tetrahydronaphthalenes: TU, therapeutic use
CN 0 (**A 86929**); 0 (Antiparkinson Agents); 0 (Dopamine Agonists); 0 (Pyridines); 0 (Receptors, Dopamine D1); 0 (Tetrahydronaphthalenes)

L97 ANSWER 24 OF 44 MEDLINE
AN 97018070 MEDLINE
DN 97018070 PubMed ID: 8864687
TI Dopamine D1 receptor desensitization profile in MPTP-lesioned primates.
AU Blanchet P J; Grondin R; Bedard P J; Shiosaki K; Britton D R
CS Neurobiology Research Centre, Hopital de l-Enfant-Jesus, Quebec City (Quebec), Canada.
SO EUROPEAN JOURNAL OF PHARMACOLOGY, **(1996 Aug 1)** 309 (1) 13-20.
Journal code: 1254354. ISSN: 0014-2999.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199701
ED Entered STN: 19970219
Last Updated on STN: 19970219
Entered Medline: 19970131
AB The motor effects of dopamine D1 receptor activation and the optimal way to stimulate these receptors were studied in a primate model of parkinsonism induced by the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), using 2 selective full dopamine D1 receptor agonists: A-77636 ([1 R,3S] 3-(1'-adamantyl)-1-aminomethyl-3,4-dihydro-5,6-dihydroxy-1 H-2-benzopyran hydrochloride), and **SKF 82958** (6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1 H-3-benzazepine hydrobromide). A-77636 was administered to one group of primed monkeys (N = 4) previously treated with levodopa and other dopamine receptor agonists, while **SKF 82958** was given to another group of drug-naive monkeys (N = 3). These drugs have different durations of efficacy, lasting > 20 h and approximately 1 h, respectively, and were administered once daily (A-77636) or thrice daily (**SKF 82958**) for 7 days. Both drugs demonstrated excellent antiparkinsonian efficacy and locomotor stimulation. However, a rapid, functionally important, homologous (selective for D1 receptor agonists) desensitization process took place as early as on the second day with the longer-acting drug and a dose escalation of A-77636 failed to restore the initial benefit. Thrice daily dosing at a 4-h interval with the short-acting agent **SKF 82958** maintained the maximal antiparkinsonian response but some shortening in the duration of response was observed after several days. These behavioral results show that dopamine D1 receptors are susceptible to desensitization after prolonged occupancy and can be desensitized profoundly and independently of dopamine D2 receptors in vivo in this model. Potent dopamine D1 receptor agonists with an intermediate half-life may prove to be better adjuncts in the treatment of Parkinson's disease. Clinical entities with pathologically enhanced dopamine D1 receptor-linked neural transmission might eventually also benefit from such desensitization.
CT Check Tags: Animal; Female; Support, Non-U.S. Gov't

*1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine: PD, pharmacology
*Adamantane: AA, analogs & derivatives
Adamantane: PD, pharmacology
*Benzopyrans: PD, pharmacology
Disease Models, Animal
*Dopamine Agonists: PD, pharmacology
Dose-Response Relationship, Drug
*Locomotion: DE, drug effects
Macaca
***Parkinson Disease: PP, physiopathology**
*Receptors, Dopamine D1: PH, physiology
RN 145307-34-2 (A 77636); 281-23-2 (Adamantane); 28289-54-5 (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine)
CN 0 (Benzopyrans); 0 (Dopamine Agonists); 0 (Receptors, Dopamine D1)

L97 ANSWER 25 OF 44 MEDLINE
AN 96377023 MEDLINE
DN 96377023 PubMed ID: 8782872
TI Dyskinesias and tolerance induced by chronic treatment with a D1 agonist administered in pulsatile or continuous mode do not correlate with changes of putaminal D1 receptors in drug-naive MPTP monkeys.
AU Goulet M; Grondin R; Blanchet P J; Bedard P J; Di Paolo T
CS School of Pharmacy, Laval University, Ste-Foy, Quebec, Canada.
SO BRAIN RESEARCH, **(1996 May 6)** 719 (1-2) 129-37.
Journal code: 0045503. ISSN: 0006-8993.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199702
ED Entered STN: 19970219
Last Updated on STN: 20000303
Entered Medline: 19970204
AB Nine monkeys (Macaca fascicularis) were rendered parkinsonian after intravenous administration of the toxin MPTP. Three of these animals received pulsatile administration of the D1 receptor agonist **SKF 82958** (1 mg/kg, three times daily) while three were treated by continuous infusion via an osmotic mini-pump with **SKF 82958** (at an equivalent amount daily) for 29 days. Untreated MPTP as well as healthy control animals were also studied. Relief of parkinsonian symptoms was observed in the three animals of the pulsatile group. However, dyskinesia occurred in two monkeys which had striatal dopamine depletion of > 99% compared to the non-dyskinetic animal slightly less denervated (94%). Monkeys receiving continuous **SKF 82958** showed no anti-parkinsonian effect and no dyskinesia. All monkeys from the pulsatile and continuous group had measurable amount of plasma **SKF 82958** as assayed by HPLC with electrochemical detection. In the putamen of all **SKF 82958**-treated monkeys, Bmax of D1 receptors labeled with [3H]SCH 23390 were increased versus untreated MPTP-monkeys with no change in Kd. In contrast, a decrease D1 receptor density was observed in the nucleus accumbens of untreated MPTP monkeys versus controls and this was not corrected with either pulsatile or continuous **SKF 82958** treatments. D2 receptor density measured with [3H]spiperone binding was increased in the posterior putamen of **SKF 82958** -treated monkeys whereas no change was observed in the accumbens compared to control animals. Hence, tolerance with the continuous administration of a D1 agonist is not associated with a decrease of putaminal D1 or D2 receptor densities and dyskinesia could not be specifically associated with an increase of putaminal D1 receptors.
CT Check Tags: Animal; Comparative Study; Female; Support, Non-U.S. Gov't
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
Benzazepines: BL, blood

*Benzazepines: PD, pharmacology
Catecholamines: ME, metabolism
Dopamine Agonists: BL, blood
*Dopamine Agonists: PD, pharmacology
Drug Administration Schedule
Drug Tolerance
*Dyskinesia, Drug-Induced: ET, etiology
Infusion Pumps, Implantable
Injections, Subcutaneous
Macaca fascicularis
Motor Activity: DE, drug effects
***Parkinson Disease, Secondary: CI, chemically induced**
*Putamen: DE, drug effects
Putamen: ME, metabolism
*Receptors, Dopamine D1: AG, agonists
RN 28289-54-5 (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine); **80751-65-1 (SK&F 82958)**
CN 0 (Benzazepines); 0 (Catecholamines); 0 (Dopamine Agonists); 0 (Receptors, Dopamine D1)

L97 ANSWER 26 OF 44 MEDLINE
AN 96366960 MEDLINE
DN 96366960 PubMed ID: 8771074
TI Dyskinesia and wearing-off following dopamine D1 agonist treatment in drug-naive 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned primates.
AU Blanchet P J; Grondin R; Bedard P J
CS Neurobiology Research Centre, Hopital de l'Enfant-Jesus, Quebec City, Canada.
SO MOVEMENT DISORDERS, **(1996 Jan)** 11 (1) 91-4.
Journal code: 8610688. ISSN: 0885-3185.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199609
ED Entered STN: 19961008
Last Updated on STN: 20000303
Entered Medline: 19960926
AB The motor effects of the short-acting, full D1 agonist **SKF 82958** were studied in three drug-naive, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned, parkinsonian monkeys treated for 4 weeks. D1 receptor stimulation with **SKF 82958** effectively relieved parkinsonism but induced choreic dyskinesia (n = 2) and a shorter duration of motor benefit (n = 3) over time. Isolated, short-lived D1 receptor activation would not appear to confer advantage over levodopa for dyskinesia prevention. Our data also support the involvement of postsynaptic dopamine receptor mechanisms in the wearing-off phenomenon seen in levodopa-treated parkinsonian patients.
CT Check Tags: Animal; Female; Support, Non-U.S. Gov't
*1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine: PD, pharmacology
*Benzazepines: PD, pharmacology
Brain: DE, drug effects
Brain: PP, physiopathology
*Dopamine Agents: PD, pharmacology
*Dopamine Agonists: PD, pharmacology
*Dyskinesia, Drug-Induced: PP, physiopathology
Levodopa: PD, pharmacology
Macaca fascicularis
*Motor Skills: DE, drug effects
Motor Skills: PH, physiology
Neurologic Examination: DE, drug effects
***Parkinson Disease, Secondary: CI, chemically induced**
Parkinson Disease, Secondary: PP, physiopathology

*Receptors, Dopamine D1: DE, drug effects
Receptors, Dopamine D1: PH, physiology
RN 28289-54-5 (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine); **80751-65-1 (SK&F 82958)**
CN 0 (Benzazepines); 0 (Dopamine Agents); 0 (Dopamine Agonists); 0 (Levodopa); 0 (Receptors, Dopamine D1)

L97 ANSWER 27 OF 44 MEDLINE
AN 96325519 MEDLINE
DN 96325519 PubMed ID: 8714707
TI Chronic alterations in dopaminergic neurotransmission produce a persistent elevation of deltaFosB-like protein(s) in both the rodent and primate striatum.
AU Doucet J P; Nakabeppu Y; Bedard P J; Hope B T; Nestler E J; Jasmin B J; Chen J S; Iadarola M J; St-Jean M; Wigle N; Blanchet P; Grondin R; Robertson G S
CS Department of Pharmacology, University of Ottawa, Ottawa, Ontario, Canada K1H 8M5.
SO EUROPEAN JOURNAL OF NEUROSCIENCE, **(1996 Feb)** 8 (2) 365-81.
Journal code: 8918110. ISSN: 0953-816X.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199610
ED Entered STN: 19961106
Last Updated on STN: 20000303
Entered Medline: 19961022
AB Using an antibody that recognizes the products of all known members of the fos family of immediate early genes, it was demonstrated that destruction of the nigrostriatal pathway by 6-hydroxydopamine (6-OHDA) lesions of the medial forebrain bundle produces a prolonged (>3 months) elevation of Fos-like immunoreactivity in the striatum. Using retrograde tract tracing techniques, we have previously shown that this increase in Fos-like immunoreactivity is located predominantly in striatal neurons that project to the globus pallidus. In the present study, Western blots were performed on nuclear extracts from the intact and denervated striatum of 6-OHDA-lesioned rats to determine the nature of Fos-immunoreactive protein(s) responsible for this increase. Approximately 6 weeks after the 6-OHDA lesion, expression of two Fos-related antigens with apparent molecular masses of 43 and 45 kDa was enhanced in the denervated striatum. Chronic haloperidol administration also selectively elevated expression of these Fos-related antigens, suggesting that their induction after dopaminergic denervation is mediated by reduced activation of D2-like dopamine receptors. Western blot immunostaining using an antibody which recognizes the N-terminus of FosB indicated that the 43 and 45 kDa Fos-related antigens induced by dopaminergic denervation and chronic haloperidol administration may be related to a truncated form of FosB known as deltaFosB. Consistent with this proposal, retrograde tracing experiments confirmed that deltaFosB-like immunoreactivity in the deafferented striatum was located predominantly in striatopallidal neurons. Gel shift experiments demonstrated that elevated AP-1 binding activity in denervated striata contained FosB-like protein(s), suggesting that enhanced deltaFosB levels may mediate some of the effects of prolonged dopamine depletion on AP-1-regulated genes in striatopallidal neurons. In contrast, chronic administration of the D1-like receptor agonist CY 208243 to 6-OHDA-lesioned rats dramatically enhanced deltaFosB-like immunoreactivity in striatal neurons projecting to the substantia nigra. Western blot immunostaining revealed that deltaFosB and, to a lesser extent, FosB are elevated by chronic D1-like agonist administration. Both the quantitative reverse transcriptase-polymerase chain reaction and the ribonuclease protection assay demonstrated that deltafosB mRNA levels were substantially enhanced in the denervated

striatum by chronic D1-like agonist administration. Lastly, we examined the effects of chronic administration ofD1-like and D2-like dopamine receptor agonists on striatal deltaFosB expression in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) primate model of Parkinson's disease. In monkeys rendered Parkinsonian by MPTP, there was a modest increase in deltaFosB-like protein(s), while the development of dyskinesia produced by chronic D1-like agonist administration was accompanied by large increases in DeltaFosB-like protein(s). In contrast, administration of the long-acting D2-like agonist cabergoline, which alleviated Parkinsonian symptoms without producing dyskinesia reduced deltaFosB levels to near normal. Taken together, these results demonstrate that chronic alterations in dopaminergic neurotransmission produce a persistent elevation of deltaFosB-like protein(s) in both the rodent and primate striatum.

CT Check Tags: Animal; Comparative Study; Female; Male; Support, Non-U.S. Gov't
*Bacterial Proteins: BI, biosynthesis
Bacterial Proteins: GE, genetics
Base Sequence
Benzazepines: PD, pharmacology
Blotting, Western
Corpus Striatum: DE, drug effects
*Corpus Striatum: ME, metabolism
Denervation
*Dopamine Agonists: PD, pharmacology
*Dopamine Antagonists: TO, toxicity
Ergolines: PD, pharmacology
*Gene Expression Regulation: DE, drug effects
*Genes, fos
Haloperidol: TO, toxicity
Indoles: PD, pharmacology
MPTP Poisoning
Macaca fascicularis
Molecular Weight
*Nerve Tissue Proteins: BI, biosynthesis
Nerve Tissue Proteins: GE, genetics
*Oxidopamine: TO, toxicity
Parkinson Disease, Secondary: CI, chemically induced
Parkinson Disease, Secondary: ME, metabolism
Phenanthridines: PD, pharmacology
Polymerase Chain Reaction
RNA, Messenger: BI, biosynthesis
Rats
Rats, Wistar
Receptors, Dopamine D1: AG, agonists
Receptors, Dopamine D2: AI, antagonists & inhibitors
Species Specificity
Time Factors

RN 100999-26-6 (CY 208-243); 1199-18-4 (Oxidopamine); 52-86-8 (Haloperidol); **80751-65-1 (SK&F 82958); 81409-90-7 (cabergoline)**

CN 0 (Bacterial Proteins); 0 (Benzazepines); 0 (Dopamine Agonists); 0 (Dopamine Antagonists); 0 (Ergolines); 0 (Indoles); 0 (Nerve Tissue Proteins); 0 (Phenanthridines); 0 (RNA, Messenger); 0 (Receptors, Dopamine D1); 0 (Receptors, Dopamine D2); 0 (fosB protein)

L97 ANSWER 28 OF 44 MEDLINE
AN 96135061 MEDLINE
DN 96135061 PubMed ID: 8558425
TI ABT-431: the diacetyl prodrug of **A-86929**, a potent and selective dopamine D1 receptor agonist: in vitro characterization and effects in animal models of Parkinson's disease.
AU Shiosaki K; Jenner P; Asin K E; Britton D R; Lin C W; Michaelides M; Smith L; Bianchi B; Didomenico S; Hodges L; Hong Y; Mahan L; Mikusa J; Miller T;

Nikkel A; Stashko M; Witte D; Williams M
CS Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, Illinois, USA.
SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, **(1996 Jan)** 276 (1) 150-60.
Journal code: 0376362. ISSN: 0022-3565.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199602
ED Entered STN: 19960312
Last Updated on STN: 20000303
Entered Medline: 19960226
AB (-)-Trans 9,10-hydroxy-2-propyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[c]phenanthrene hydrochloride (**A-86929**) is a potent and selective full agonist at the dopamine (DA) D1-like receptor. Judging by its binding affinities to the D1 and D2 classes of receptors, the compound is approximately 20-fold D1 receptor-selective, whereas relative potencies based on functional in vitro assays indicate that **A-86929** is greater than 400-fold D1-selective. **A-86929** has moderate to weak (Ki > 1 microM) affinity at other monoaminergic and peptidergic receptors, at ion channels and at monoamine uptake sites. The catechol of **A-86929** was bis-acetylated to produce the prodrug, (-)-trans 9,10-acetoxy-2-propyl-4,5,5a,6,7,11-b-hexahydro-3-thia- 5-azacyclopent-1-ena[c]phenanthrene hydrochloride (ABT-431), which is more chemically stable yet is rapidly converted to the parent compound with a half-life of less than 1 min in plasma. Both **A-86929** and ABT-431 produced contralateral rotation in rats bearing unilateral 6-hydroxydopamine lesions, with ED50 values of 0.24 mumol/kg s.c. and 0.54 mumol/kg s.c., respectively. **A-86929** and ABT-431 improved behavioral disability scores and increased locomotor activity in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned marmoset model of Parkinson's disease in a dose-dependent manner (the minimum effective dose was 0.10 mumol/kg s.c.). When administered three times daily for 30 consecutive days to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned marmosets, **A-86929** significantly improved disability scores throughout the duration of the study. Current Parkinson's disease therapy includes L-dopa, which stimulates both classes of DA receptors by virtue of its conversion to DA in vivo, and direct-acting D2-selective agonists. Stimulation of the D2 receptor, which is associated with all current DA agonist-based therapies, may contribute to their dose-limiting side effects. An agent such as **A-86929** (or its prodrug ABT-431), which selectively stimulates the D1 receptor, may represent a novel mechanism for Parkinson's disease therapy with the potential for an improved side-effect profile and, consequently, improved patient compliance.
CT Check Tags: Animal; Female; Human; Male
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
Antiparkinson Agents: ME, metabolism
*Antiparkinson Agents: PD, pharmacology
Behavior, Animal: DE, drug effects
CHO Cells
Callithrix
Corpus Striatum: ME, metabolism
Corpus Striatum: UL, ultrastructure
Disease Models, Animal
Dopamine Agonists: ME, metabolism
*Dopamine Agonists: PD, pharmacology
Dose-Response Relationship, Drug
Fishes
Hamsters

Kinetics
Mice
Parkinson Disease, Secondary: CI, chemically induced
***Parkinson Disease, Secondary: DT, drug therapy**
Parkinson Disease, Secondary: ME, metabolism
Prodrugs: ME, metabolism
*Prodrugs: PD, pharmacology
Pyridines: ME, metabolism
*Pyridines: PD, pharmacology
Rats
Rats, Sprague-Dawley
*Receptors, Dopamine D1: AG, agonists
Receptors, Dopamine D1: ME, metabolism
Tetrahydronaphthalenes: ME, metabolism
*Tetrahydronaphthalenes: PD, pharmacology
RN 28289-54-5 (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine)
CN 0 (**A 86929**); 0 (ABT 431); 0 (Antiparkinson Agents); 0 (Dopamine Agonists); 0 (Prodrugs); 0 (Pyridines); 0 (Receptors, Dopamine D1); 0 (Tetrahydronaphthalenes)

L97 ANSWER 29 OF 44 MEDLINE
AN 96057156 MEDLINE
DN 96057156 PubMed ID: 7566481
TI "Full" dopamine D1 agonists in human caudate: biochemical properties and therapeutic implications.
AU Gilmore J H; Watts V J; Lawler C P; Noll E P; Nichols D E; Mailman R B
CS Department of Psychiatry, University of North Carolina School of Medicine, Chapel Hill 27599-7160, USA.
NC MH40537 (NIMH)
MH42705 (NIMH)
MH50356 (NIMH)
SO NEUROPHARMACOLOGY, **(1995 May)** 34 (5) 481-8.
Journal code: 0236217. ISSN: 0028-3908.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199511
ED Entered STN: 19951227
Last Updated on STN: 19980206
Entered Medline: 19951122
AB Recent data indicate that full D1 dopamine agonists have greater antiparkinsonian effects in the MPTP primate model than do partial agonists, suggesting that the intrinsic activity of D1 agonists may affect their utility in the treatment of Parkinson's disease. It is unclear, however, whether human D1 receptors in situ are similar to D1 receptors in other species or in molecular expression systems. For this reason, the binding affinity and functional activity of a series of D1 dopamine receptor agonists [**dihydrexidine** (DHX), **SKF82958**, and A68930] were determined in postmortem human caudate. Results from in vitro binding studies with membranes from human caudate indicate that these D1 agonists competed for [3H]SCH23390 labeled sites with a rank order similar to that found in rat striatum [K50 = 36.8 nM (DHX); 18.6 nM (**SKF82958**); 3.9 nM (A68930)]. The ability of these compounds and the partial agonist SKF38393 to stimulate the enzyme adenylyl cyclase in tissue homogenates of human caudate was also examined. DHX and A68930 are full agonists compared to dopamine, whereas **SKF82958** and SKF38393 are partial agonists. These differences in biochemical intrinsic activity are consistent with the profound antiparkinsonian effects caused by DHX, but not by **SKF82958** and SKF38393, in the MPTP-monkey model. This suggests that DHX and A68930 may be of greater utility in treating disorders where a full efficacy D1 agonist may be required.
CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.

Adenylate Cyclase: DE, drug effects
Autopsy
Benzazepines: PD, pharmacology
Binding, Competitive
*Caudate Nucleus: DE, drug effects
Dopamine: PD, pharmacology
*Dopamine Agonists: PD, pharmacology
Dose-Response Relationship, Drug
Parkinson Disease
*Receptors, Dopamine D1: DE, drug effects
Sch-23390: PD, pharmacology
RN 51-61-6 (Dopamine); **80751-65-1 (SK&F 82958)**; 87075-17-0 (Sch-23390)
CN 0 (Benzazepines); 0 (Dopamine Agonists); 0 (Receptors, Dopamine D1); EC 4.6.1.1 (Adenylate Cyclase)

L97 ANSWER 30 OF 44 MEDLINE
AN 95406265 MEDLINE
DN 95406265 PubMed ID: 7675833
TI **Dihydrexidine**, a full D1 dopamine receptor agonist, induces rotational asymmetry in hemiparkinsonian monkeys.
AU Johnson B J; Peacock V; Schneider J S
CS Department of Neurology, Hahnemann University, Philadelphia, PA 19102, USA.
NC MH 46531 (NIMH)
SO PHARMACOLOGY, BIOCHEMISTRY AND BEHAVIOR, **(1995 Aug)** 51 (4) 617-22.
Journal code: 0367050. ISSN: 0091-3057.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199510
ED Entered STN: 19951026
Last Updated on STN: 20000303
Entered Medline: 19951019
AB **Dihydrexidine** (trans-10,11-dihydroxy5,6,6a,7,8,12b hexanhyydrobenso- [alpha]phenanthridine) is a full dopamine D1 agonist. In rhesus macaque monkeys rendered hemiparkinsonian by unilateral intracarotid infusions of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), **dihydrexidine** (0.15-0.9 mg/kg) elicited dose-dependent contralateral rotation. The effects of **dihydrexidine** were blocked by pretreatment with the D1 antagonist SCH 23390 (0.03 mg/kg), but not by the D2 antagonist raclopride (0.025 mg/kg). These results suggest a functional role for D1 receptors in stimulating motor behavior in a primate model of Parkinson's disease.
CT Check Tags: Animal; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
*Behavior, Animal: DE, drug effects
Dose-Response Relationship, Drug
Ergolines: PD, pharmacology
*Laterality: DE, drug effects
Macaca mulatta
Parkinson Disease, Secondary: CI, chemically induced
***Parkinson Disease, Secondary: PX, psychology**
Phenanthridines: AI, antagonists & inhibitors
*Phenanthridines: PD, pharmacology
Quinpirole
Raclopride
*Receptors, Dopamine D1: AG, agonists
Receptors, Dopamine D1: AI, antagonists & inhibitors
Receptors, Dopamine D2: AI, antagonists & inhibitors

Rotation
Salicylamides: PD, pharmacology
Sch-23390: PD, pharmacology
RN **123039-93-0 (dihydrexidine)**; 28289-54-5 (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine); 84225-95-6 (Raclopride); 85760-74-3 (Quinpirole); 87075-17-0 (Sch-23390)
CN 0 (Ergolines); 0 (Phenanthridines); 0 (Receptors, Dopamine D1); 0 (Receptors, Dopamine D2); 0 (Salicylamides)

L97 ANSWER 31 OF 44 MEDLINE
AN 95341804 MEDLINE
DN 95341804 PubMed ID: 7616686
TI Behavioral involvement of central dopamine D1 and D2 receptors in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned parkinsonian cynomolgus monkeys.
AU Akai T; Ozawa M; Yamaguchi M; Mizuta E; Kuno S
CS Research Department, Nihon Schering K.K., Osaka, Japan.
SO JAPANESE JOURNAL OF PHARMACOLOGY, **(1995 Feb)** 67 (2) 117-24.
Journal code: 2983305R. ISSN: 0021-5198.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199508
ED Entered STN: 19950905
Last Updated on STN: 20000303
Entered Medline: 19950824
AB To clarify the roles of dopamine D1 and D2 receptors in behavioral symptoms of Parkinson's disease, antiparkinsonian effects of various dopamine agonists in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned parkinsonian monkeys were investigated with regard to induction of hyperactivity such as excitability, irritability and aggressiveness. The non-selective dopamine agonist apomorphine ameliorated the parkinsonism, but induced marked hyperactivity dose-dependently. Pretreatment with either the dopamine D1 antagonist SCH 23390 or the dopamine D2 antagonist sulpiride markedly suppressed the apomorphine-induced hyperactivity with slight attenuation of the antiparkinsonian effects. Both the dopamine D2-receptor agonist quinpirole and the dopamine D1-receptor agonist **SKF 82958** ameliorated the parkinsonism in a dose-dependent manner with a slight induction of hyperactivity. Combination treatment of a threshold dose of quinpirole with that of **SKF 82958** augmented the antiparkinsonian effects without a marked induction of hyperactivity. However, the combination treatment at higher doses induced marked hyperactivity accompanied by augmented antiparkinsonian effects. These results suggest that stimulation of either central dopamine D1 or D2 receptors is requisite for the antiparkinsonian effects and concurrent strong stimulation of both central dopamine D1 and D2 receptors causes marked hyperactivity which may be predictive of dopaminergic psychiatric side effects.
CT Check Tags: Animal
*1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine: PD, pharmacology
Apomorphine: PD, pharmacology
Behavior, Animal
Disease Models, Animal
Dose-Response Relationship, Drug
Macaca fascicularis
Parkinson Disease, Secondary
*Receptors, Dopamine D1: PH, physiology
*Receptors, Dopamine D2: PH, physiology
Sulpiride: PD, pharmacology
Time Factors
RN 15676-16-1 (Sulpiride); 28289-54-5 (1-Methyl-4-phenyl-1,2,3,6-

tetrahydropyridine); 58-00-4 (Apomorphine)
CN 0 (Receptors, Dopamine D1); 0 (Receptors, Dopamine D2)

L97 ANSWER 32 OF 44 MEDLINE
AN 95288444 MEDLINE
DN 95288444 PubMed ID: 7770604
TI The differential behavioural effects of benzazepine D1 dopamine agonists with varying efficacies, co-administered with quinpirole in primate and rodent models of Parkinson's disease.
AU Gnanalingham K K; Hunter A J; Jenner P; Marsden C D
CS Parkinson's Disease Society, Experimental Research Laboratories, King's College, London, U.K.
SO PSYCHOPHARMACOLOGY, **(1995 Feb)** 117 (3) 287-97.
Journal code: 7608025. ISSN: 0033-3158.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199507
ED Entered STN: 19950713
Last Updated on STN: 20000303
Entered Medline: 19950706
AB The effects of co-administration of quinpirole with benzazepine D1 dopamine (DA) agonists possessing full/supramaximal (SKF 80723 and **SKF 82958**), partial (SKF 38393 and SKF 75670) and no efficacies (SKF 83959) in stimulating adenylate cyclase (AC) were investigated in rodent and primate models of Parkinson's disease (PD). In rats with a unilateral 6-hydroxydopamine (6-OHDA) lesion of the medial forebrain bundle, co-administration of SKF 38393 (7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine), SKF 75670 (3-CH3 analogue), SKF 80723 (6-Br analogue), SKF 83959 (6-Cl, 3-CH3, 3'-CH3 analogue) and **SKF 82958** (6-Cl, 3-C3H5 analogue) strongly potentiated the contralateral circling induced by quinpirole. In MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) treated common marmosets, administration of quinpirole alone increased locomotor activity and reversed motor deficits. Grooming and oral activity were unaltered. Co-administration of SKF 38393 and SKF 75670 inhibited the quinpirole-induced changes in locomotor activity and motor disability. The combined treatment of SKF 80723 or **SKF 82958** with quinpirole had no overall effect on locomotor activity or motor disability. In contrast, SKF 83959 extended the duration of the quinpirole-induced increase in locomotor activity with corresponding decreases in motor disability. Co-administration of high doses of **SKF 82958** and more especially SKF 83959 and SKF 80723, with quinpirole induced hyperexcitability and seizures. Oral activity and grooming were unaltered following the co-administration of benzazepine derivatives with quinpirole. The ability of some benzazepine D1 DA agonists to prolong the antiparkinsonian effects of quinpirole in the MPTP-treated marmoset may indicate a role for certain D1 DA agonists in the clinical treatment of PD. In general, the behavioural responses to the combined administration of benzazepines with quinpirole in the 6-OHDA lesioned rat and more especially the MPTP-treated marmoset failed to correlate with their ability to stimulate AC. These observations further implicate a behavioural role for D1 DA receptors not linked to AC.
CT Check Tags: Animal; Female; In Vitro; Male; Support, Non-U.S. Gov't
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
Adenylate Cyclase: ME, metabolism
*Behavior, Animal: DE, drug effects
Callithrix
*Dopamine Agonists: TU, therapeutic use
*Ergolines: TU, therapeutic use
Parkinson Disease, Secondary: CI, chemically induced
***Parkinson Disease, Secondary: DT, drug therapy**

Quinpirole
Rats
Rats, Wistar
*Receptors, Dopamine D1: AG, agonists
Species Specificity
RN 28289-54-5 (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine); 85760-74-3 (Quinpirole)
CN 0 (Dopamine Agonists); 0 (Ergolines); 0 (Receptors, Dopamine D1); EC 4.6.1.1 (Adenylate Cyclase)

L97 ANSWER 33 OF 44 MEDLINE
AN 95288443 MEDLINE
DN 95288443 PubMed ID: 7770603
TI Differential anti-parkinsonian effects of benzazepine D1 dopamine agonists with varying efficacies in the MPTP-treated common marmoset.
AU Gnanalingham K K; Erol D D; Hunter A J; Smith L A; Jenner P; Marsden C D
CS Parkinson's Disease Society Experimental Research Laboratories, King's College London, UK.
SO PSYCHOPHARMACOLOGY, **(1995 Feb)** 117 (3) 275-86.
Journal code: 7608025. ISSN: 0033-3158.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199507
ED Entered STN: 19950713
Last Updated on STN: 20000303
Entered Medline: 19950706
AB In common marmosets systemically treated with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), the behavioural effects of benzazepine D1 dopamine (DA) agonists with full/supramaximal (SKF 80723 and **SKF 82958**), partial (SKF 38393, SKF 75670 and SKF 83565) and no efficacies (SKF 83959) in stimulating adenylate cyclase (AC) activity were investigated. The benzazepine derivatives, with the exception of **SKF 82958** (8 fold D1 DA receptor selectivity), demonstrated high D1 DA receptor affinity and selectivity (approximately 100 fold or more) in rat striatal homogenates. Administration of MPTP in marmosets induced locomotor hypoactivity, rigidity and motor disability. SKF 38393 (7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3- benzazepine) and SKF 75670 (3-CH3 analogue) further reduced locomotor activity (by -70 to -80%) and increased motor disability (by +22 to +67%) in these animals. SKF 83565 (6-Cl, 3-CH3, 3'-Cl analogue) and **SKF 82958** (6-Cl, 3-C3H5 analogue) had only a slight effect on locomotor activity but decreased motor disability at high doses (-46 to -60%). In contrast, SKF 83959 (6-Cl, 3-CH3, 3'-CH3 analogue) and SKF 80723 (6-Br analogue) produced pronounced increases in locomotion (6-10 fold) and a reversal in motor disability (by -64 to -77%). Oral activity, consisting largely of abnormal, 'dyskinetic' tongue protrusions and vacuous chews, was increased in animals treated with SKF 38393, SKF 83565, **SKF 82958** and more especially with SKF 80723 and SKF 83959. Grooming was increased with **SKF 82958** and more especially with SKF 80723 and SKF 83959. In contrast, quinpirole (D2 DA agonist), reversed the MPTP-induced motor deficits in the marmoset, with no effect on grooming and oral activity. The present findings further demonstrate the antiparkinsonian actions of some D1 DA agonists in MPTP-treated primates. However, in general the behavioural effects of benzazepines failed to correlate with either their D1 DA receptor affinity/selectivity or their efficacy in stimulating adenylate cyclase (AC) activity. These observations further implicate a behavioural role for D1 DA receptors uncoupled to AC and/or a role for extrastriatal D1 DA receptors in mediating the behavioural response to D1 DA agonists.
CT Check Tags: Animal; In Vitro; Male; Support, Non-U.S. Gov't
*1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine

*Antiparkinson Agents: PD, pharmacology
Behavior, Animal: DE, drug effects
Binding, Competitive: DE, drug effects
Callithrix
Dopamine Agonists: ME, metabolism
*Dopamine Agonists: TU, therapeutic use
Ergolines: PD, pharmacology
Parkinson Disease, Secondary: CI, chemically induced
***Parkinson Disease, Secondary: DT, drug therapy**
Parkinson Disease, Secondary: PX, psychology
Quinpirole
Radioligand Assay
Rats
Rats, Wistar
*Receptors, Dopamine D1: AG, agonists
Receptors, Dopamine D1: ME, metabolism
Receptors, Dopamine D2: ME, metabolism
Sch-23390: ME, metabolism
Spiperone: ME, metabolism
RN 28289-54-5 (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine); 749-02-0 (Spiperone); 85760-74-3 (Quinpirole); 87075-17-0 (Sch-23390)
CN 0 (Antiparkinson Agents); 0 (Dopamine Agonists); 0 (Ergolines); 0 (Receptors, Dopamine D1); 0 (Receptors, Dopamine D2)

L97 ANSWER 34 OF 44 MEDLINE
AN 95230555 MEDLINE
DN 95230555 PubMed ID: 7714782
TI Combination treatment of the partial D2 agonist terguride with the D1 agonist **SKF 82958** in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned parkinsonian cynomolgus monkeys.
AU Akai T; Ozawa M; Yamaguchi M; Mizuta E; Kuno S
CS Research Department, Institute of Pharma Research, Development and Medical Science, Osaka, Japan.
SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, **(1995 Apr)** 273 (1) 309-14.
Journal code: 0376362. ISSN: 0022-3565.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199505
ED Entered STN: 19950524
Last Updated on STN: 19950524
Entered Medline: 19950517
AB The optimal combination of a dopamine D2 agonist and a D1 agonist was evaluated for symptomatic treatment of Parkinson's disease. Behavioral effects of combination treatment of the full D2 agonist quinpirole or the partial D2 agonist terguride with the full D1 agonist **SKF 82958** [(I) 6-Chloro-7, 8-dihydroxy-3-allyl-1-phenyl-2, 3, 4, 5-tetra-hydro-1H-3-benzazepine] were investigated in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned parkinsonian cynomolgus monkeys with attention to the induction of hyperactivity such as irritability, excitability and aggressiveness and of dyskinesias such as licking of paws, chewing and biting. Both quinpirole and **SKF 82958** alone improved the parkinsonism with a slight induction of the hyperactivity and dyskinesias. Terguride also improved the parkinsonism but did not induce the hyperactivity and dyskinesias. Combination treatment of quinpirole with **SKF 82958** not only showed a tendency to augment the antiparkinsonian effects but also induced the marked hyperactivity and dyskinesias. On the other hand, combination treatment of terguride with **SKF 82958** also augmented the antiparkinsonian effects but did not induce any hyperactivity and dyskinesias. These findings suggest that combination therapy with a

partial D2 agonist and a full D1 agonist or monotherapy with a dopamine agonist that has both partial D2 and full D1 agonist properties might be beneficial for treating motor dysfunction in Parkinson's disease without inducing dopaminergic side effects.

CT Check Tags: Animal
*Benzazepines: AD, administration & dosage
*Dopamine Agonists: AD, administration & dosage
Drug Therapy, Combination
Lisuride: AD, administration & dosage
*Lisuride: AA, analogs & derivatives
***MPTP Poisoning**
Macaca fascicularis
***Parkinson Disease: DT, drug therapy**
*Receptors, Dopamine D1: AG, agonists
*Receptors, Dopamine D2: AG, agonists

RN 18016-80-3 (Lisuride); 37686-84-3 (dironyl); **80751-65-1 (SK&F 82958)**

CN 0 (Benzazepines); 0 (Dopamine Agonists); 0 (Receptors, Dopamine D1); 0 (Receptors, Dopamine D2)

L97 ANSWER 35 OF 44 MEDLINE
AN 95153319 MEDLINE
DN 95153319 PubMed ID: 7850462
TI Effects of **dihydrexidine**, a full dopamine D-1 receptor agonist, on delayed response performance in chronic low dose MPTP-treated monkeys.
AU Schneider J S; Sun Z Q; Roeltgen D P
CS Center for Neurological Research of the Department of Neurology, Hahnemann University, Philadelphia, PA 19102.
NC MH-46531 (NIMH)
SO BRAIN RESEARCH, **(1994 Nov 7)** 663 (1) 140-4.
Journal code: 0045503. ISSN: 0006-8993.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199503
ED Entered STN: 19950322
Last Updated on STN: 20000303
Entered Medline: 19950314

AB Monkeys exposed to low doses of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) over long periods of time develop cognitive deficits without severe parkinsonian motor signs. In the present study we assessed the effects of the selective and full dopamine D-1 receptor agonist **dihydrexidine** on delayed response deficits in chronic low dose (CLD) MPTP-treated monkeys. **Dihydrexidine** caused a dose-dependent improvement in task performance, that could be blocked by the D-1 receptor antagonist SCH-23390. In addition to reducing the number of mistakes made during delayed response performance, **dihydrexidine** also improved task persistence. These data suggest that **dihydrexidine** may be useful in treating cognitive as well as motor deficits of parkinsonism.

CT Check Tags: Animal; Female; Male; Support, U.S. Gov't, P.H.S.
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
*Dopamine Agonists: PD, pharmacology
Dose-Response Relationship, Drug
Macaca fascicularis
Macaca nemestrina
Parkinson Disease, Secondary: CI, chemically induced
***Parkinson Disease, Secondary: PP, physiopathology**
*Phenanthridines: PD, pharmacology
*Psychomotor Performance: DE, drug effects
Random Allocation
*Receptors, Dopamine D1: AG, agonists

Sch-23390: PD, pharmacology
RN **123039-93-0 (dihydrexidine)**; 28289-54-5 (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine); 87075-17-0 (Sch-23390)
CN 0 (Dopamine Agonists); 0 (Phenanthridines); 0 (Receptors, Dopamine D1)

L97 ANSWER 36 OF 44 MEDLINE
AN 94074591 MEDLINE
DN 94074591 PubMed ID: 7902811
TI Dopamine D1 receptors: efficacy of full (**dihydrexidine**) vs. partial (SKF38393) agonists in primates vs. rodents.
AU Watts V J; Lawler C P; Gilmore J H; Southerland S B; Nichols D E; Mailman R B
CS Department of Pharmacology, University of North Carolina School of Medicine, Chapel Hill 27599-7250.
NC ES05279 (NIEHS)
MH40537 (NIMH)
MH42705 (NIMH)
+
SO EUROPEAN JOURNAL OF PHARMACOLOGY, **(1993 Sep 28)** 242 (2) 165-72.
Journal code: 1254354. ISSN: 0014-2999.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199401
ED Entered STN: 19940203
Last Updated on STN: 19980206
Entered Medline: 19940113
AB Although partial efficacy dopamine D1 receptor agonists have little therapeutic benefit in parkinsonism, the first high potency, full efficacy dopamine D1 receptor agonist **dihydrexidine** recently has been shown to have profound antiparkinsonian effects. One reason for the greater antiparkinsonian effects of **dihydrexidine** vs. SKF38393 might be that SKF38393, while a partial dopamine D1 receptor agonist in rodent striatal preparations, has virtually no agonist activity in monkey striatum (Pifl et al., 1991, Eur. J. Pharmacol. 202, 273). To explore this hypothesis, we compared the dopamine D1 receptor affinity and efficacy of **dihydrexidine** and SKF38393 in striatum from rat and monkey. In vitro binding studies using membranes from putamen of adult rhesus monkeys demonstrated that **dihydrexidine** competed for dopamine D1 receptors (labeled with [3H]SCH23390) with high potency (IC50 = 20 nM vs. ca. 10 nM in rat brain). SKF38393 was about 4-fold less potent than **dihydrexidine** in both monkey and rat brain. The in vitro functional activity of these drugs was assessed by their ability to stimulate adenylate cyclase activity in tissue homogenates. **Dihydrexidine** was of full efficacy (relative to dopamine) in stimulating cAMP synthesis in both monkey and rat. SKF38393 was only a partial efficacy agonist in both rat striatum and monkey putamen, but contrary to the original hypothesis, it had the same efficacy (ca. 40% relative to **dihydrexidine**) in membranes from both species. Interestingly, greater between-subject variation was found in the stimulation produced by SKF38393 in primate compared to rat brain, although the basis for this variation is unclear.(ABSTRACT TRUNCATED AT 250 WORDS)
CT Check Tags: Animal; Comparative Study; Male; Support, U.S. Gov't, P.H.S.
Adenylate Cyclase: ME, metabolism
*Dopamine Agents: PD, pharmacology
*Macaca mulatta
Macaca mulatta: ME, metabolism
Parkinson Disease: DT, drug therapy
*Phenanthridines: PD, pharmacology
Radioligand Assay
*Rats

Rats: ME, metabolism
Rats, Sprague-Dawley
*Receptors, Dopamine D1: DE, drug effects
*SK&F-38393: PD, pharmacology
Species Specificity
RN **123039-93-0 (dihydrexidine)**; 67287-49-4 (SK&F-38393)
CN 0 (Dopamine Agents); 0 (Phenanthridines); 0 (Receptors, Dopamine D1); EC 4.6.1.1 (Adenylate Cyclase)

L97 ANSWER 37 OF 44 MEDLINE
AN 94046545 MEDLINE
DN 94046545 PubMed ID: 7901395
TI Differential effect of selective D-1 and D-2 dopamine receptor agonists on levodopa-induced dyskinesia in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine- exposed monkeys.
AU Blanchet P; Bedard P J; Britton D R; Kebabian J W
CS Centre de recherche en neurobiologie, Hopital de l'Enfant-Jesus, Quebec, Canada.
SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, **(1993 Oct)** 267 (1) 275-9.
Journal code: 0376362. ISSN: 0022-3565.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199311
ED Entered STN: 19940117
Last Updated on STN: 19950206
Entered Medline: 19931129
AB The motor effects of selective D-1 dopamine receptor stimulation in Parkinson's disease have been explored in a limited number of studies with partial D-1 agonists only and the results were unsatisfactory. Four 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-exposed parkinsonian monkeys already exhibiting levodopa- and dopamine agonist-induced dyskinesia received selective D-1 agonists ([2,3,4,5-tetrahydro-7-8-dihydroxy-1-phenyl-1-H-3-benzazepine- HCI] (SKF 38393), [(+-)6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro- 1H-3-benzazepine hydrobromide] (**SKF 82958**), [(1R, 3S)3-(1'-adamantyl)-1-aminomethyl-3,4-dihydro-5,6- dihydroxy-1H-2-benzopyran hydrochloride] (A-77636) and [(-)-(6aR)(12bR)-4,6,6a,7,8,12b-hexahydro-7-methyli ndolo (4,3-ab)-phenanthridine] (CY 208-243)) to compare these drugs with selective D-2 agonists (LY 171555, (+)-4-propyl-9- hydroxynaphthoxazine and bromocriptine) and levodopa in terms of antiparkinsonian efficacy and side effects. The D-1 class of compounds was as efficacious as the D-2 agents in alleviating parkinsonism in these animals. However, D-1 agonists were, in general, less likely to reproduce dyskinesia. In addition, D-1 agonists occasionally improved motor symptoms without concomitant dyskinesia, unlike D-2 agonists or levodopa (which always produced some dyskinesia with improvement in motor function). These preliminary results do not support the hypothesis that preferential D-1 receptor stimulation facilitates dyskinesia in primates.(ABSTRACT TRUNCATED AT 250 WORDS)
CT Check Tags: Animal; Female; Support, Non-U.S. Gov't
Dopamine: PH, physiology
*Dopamine Agents: PD, pharmacology
*Dyskinesia, Drug-Induced: PP, physiopathology
*Levodopa: TO, toxicity
MPTP Poisoning
Macaca fascicularis
Motor Activity: DE, drug effects
***Parkinson Disease: PP, physiopathology**
*Receptors, Dopamine D1: DE, drug effects
*Receptors, Dopamine D2: DE, drug effects

RN 51-61-6 (Dopamine)
CN 0 (Dopamine Agents); 0 (Levodopa); 0 (Receptors, Dopamine D1); 0 (Receptors, Dopamine D2)

L97 ANSWER 38 OF 44 MEDLINE
AN 93286940 MEDLINE
DN 93286940 PubMed ID: 8099621
TI Relative potency and efficacy of some dopamine agonists with varying selectivities for D1 and D2 receptors in MPTP-induced hemiparkinsonian monkeys.
CM Erratum in: J Pharmacol Exp Ther 1993 Oct;267(1):566
AU Domino E F; Sheng J
CS Department of Pharmacology, University of Michigan, Ann Arbor.
SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, **(1993 Jun)** 265 (3) 1387-91.
Journal code: 0376362. ISSN: 0022-3565.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199307
ED Entered STN: 19930723
Last Updated on STN: 20000303
Entered Medline: 19930714
AB A series of dopamine agonists were studied on contraversive circling behavior in seven 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced hemiparkinsonian monkeys. The compounds selected included [1R,3S]3-(1' adamantyl)-1-aminomethyl-3,4-dihydro-5-6-dihydroxy-1H-2-benzopyran hydrochloride (A-77636), L-3,4-dihydroxyphenylalanine methyl ester hydrochloride ester (L-dopa-methyl ester), (-)-2-[N-propyl-N-(2-thienyl) ethyl-amino-5-hydroxy-tetralin]hydrochloride (N-0923), pergolide, (+)-(4aR)-trans-3,4,4a,5,6,10b-hexahydro-4-propyl-2H-n aphth[1,2-b]-1,2-oxazin-9-ol, naxagolide (PHNO), (+/-)6-chloro-7, 8-dihydroxy-2,3,4,5-tetrahydro-1-phenyl-1H-3-benzazepine hydrobromide, (+-) chloro-PB hydrobromide (SKF-81297) and (+-) 6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benza zep ine hydrobromide, (+-) chloro-APB hydrobromide (**SKF-82958**). The dose-effect relationship of each of these compounds was determined by measuring contraversive turns/120 min after an i.m. injection. There were marked differences in the potency and efficacy of the various compounds studied. The most potent compounds were the selective D2 agonists PHNO and N-0923. L-dopa methyl ester was equally effective, but much less potent. The D1 agonist A-77636 was equally effective. The D1 agonist **SKF-82958** was also effective, but less potent. In the doses studied, the D1 agonist SKF-81297 was ineffective. With the exception of L-dopa methyl ester, the greater the D1/D2 affinity ratio, the greater the 50% of maximal dose to induce contraversive circling ($r = 0.974$, $P < .05$).
CT Check Tags: Animal; Female; Support, Non-U.S. Gov't
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
Behavior, Animal: DE, drug effects
Binding Sites
Dopamine Agents: ME, metabolism
*Dopamine Agents: PD, pharmacology
Dose-Response Relationship, Drug
Macaca nemestrina
Parkinson Disease, Secondary: CI, chemically induced
***Parkinson Disease, Secondary: ME, metabolism**
*Receptors, Dopamine D1: DE, drug effects
Receptors, Dopamine D1: ME, metabolism
*Receptors, Dopamine D2: DE, drug effects
Receptors, Dopamine D2: ME, metabolism
RN 28289-54-5 (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine)

CN 0 (Dopamine Agents); 0 (Receptors, Dopamine D1); 0 (Receptors, Dopamine D2)

L97 ANSWER 39 OF 44 MEDLINE
AN 93146084 MEDLINE
DN 93146084 PubMed ID: 1362705
TI Sensitization, response fluctuation and long-term effect of **SKF-82958** and bromocriptine in the hemi-parkinsonian rat.
AU Silverman P B
CS Department of Psychiatry and Behavioral Sciences, University of Texas Health Science Center, Houston 77030-3497.
NC DA-06269 (NIDA)
SO EUROPEAN JOURNAL OF PHARMACOLOGY, **(1992 Dec 15)** 229 (2-3) 235-40.
Journal code: 1254354. ISSN: 0014-2999.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199303
ED Entered STN: 19930312
Last Updated on STN: 20000303
Entered Medline: 19930302
AB Rats with a unilateral 6-hydroxydopamine lesion of substantia nigra were treated with the dopamine agonists **SKF-82958** (D1 receptor selective) or bromocriptine (D2 receptor-selective) and their circling response recorded. Both of the compounds induced an acute episode of rotation directed away from the lesioned side. Consecutive daily treatments with either compound usually resulted in a significantly increased average response (sensitization) over a 3- to 6-day treatment period. But nearly all animals treated with low doses of either **SKF-82958** or bromocriptine exhibited one or more days when they were totally unresponsive to drug treatment. Response fluctuations thus were not exclusively associated with D1 or D2 receptor agonist treatment. When subsequently tested, undrugged, in the drug-associated environment, 2, 4 and 10 weeks after their last drug treatment, rats that had previously been treated with **SKF-82958** exhibited rapid contralateral rotation while rats that had previously been treated with bromocriptine showed no such undrugged rotation. This result is consistent with previous findings that the D1 receptor agonist, SKF-38393, but not the D2 receptor agonist, quinpirole, had long-term behavioral effect in nigral rats, and suggests that persistent motor consequences of limited treatment with dopamine receptor agonists are D1 receptor-related.
CT Check Tags: Animal; Female; Support, U.S. Gov't, P.H.S.
*Bromocriptine: PD, pharmacology
*Dopamine Agents: PD, pharmacology
Dose-Response Relationship, Drug
*Motor Activity: DE, drug effects
Oxidopamine: TO, toxicity
***Parkinson Disease, Secondary: PP, physiopathology**
Rats
Rats, Sprague-Dawley
Substantia Nigra: DE, drug effects
Substantia Nigra: PH, physiology
RN 1199-18-4 (Oxidopamine); 25614-03-3 (Bromocriptine); **80751-65-1 (SK&F 82958)**
CN 0 (Dopamine Agents)

L97 ANSWER 40 OF 44 MEDLINE
AN 93140004 MEDLINE
DN 93140004 PubMed ID: 8093726
TI N-methyl-D-aspartate receptor antagonist and dopamine D1 and D2 agonist

interactions in 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine-induced hemiparkinsonian monkeys.

AU Domino E F; Sheng J
CS Department of Pharmacology, University of Michigan, Ann Arbor.

SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, **(1993 Jan)** 264 (1) 221-5.
Journal code: 0376362. ISSN: 0022-3565.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199302
ED Entered STN: 19930312
Last Updated on STN: 20000303
Entered Medline: 19930223

AB The noncompetitive N-methyl-D-aspartate antagonist (5R,10S)-(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine hydrogen maleate (MK-801) and three dopamine agonists [(+/-)6-chloro-7,8-dihydroxy-2,3,4,5-tetrahydro-1-phenyl-1H-3-benzazepin e hydrobromide (SKF-81297), (+/-)6,chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5- tetrahydro-1H-3-benzazepine hydrobromide (**SKF-82958**) selective for D1 and (-)-2-[N-propyl-N-(2-thienyl)ethyl-amino-5- hydroxytetralin] hydrochloride (N-0923) selective for D2 receptors] were studied in seven adult female hemiparkinsonian Macaca nemestrina monkeys. Video recordings of free circling behavior showed that both **SKF-82958** and N-0923 produced dose-related mean increases in contraversive rotations during the 120-min period after i.m. injection. SKF-81297 (21.1, 67.8 and 210.7 micrograms/kg) was relatively inactive compared to **SKF-82958** (24.8, 74.8 and 234 micrograms/kg). The selective D2 agonist N-0923 (3.2, 10 and 32 micrograms/kg, i.m.) was the most potent in producing contraversive circling behavior. The noncompetitive N-methyl-D-aspartate antagonist dizocilpine (MK-801), in doses of 10 and 32 micrograms/kg i.m., produced a very slight increase in contraversive circling in contrast to the selective dopamine agonist **SKF-82958**. A large dose (100 micrograms/kg, i.m.) of MK-801 produced marked central nervous system depression. In combination with the dopamine agonists N-0923 and **SKF-82958**, MK-801 depressed contraversive circling in all doses studied. This study using hemiparkinsonian monkeys does not support the suggestion that a noncompetitive N-methyl-D-aspartate antagonist such as MK-801 would be useful in adjunctive therapy of human Parkinson's disease.

CT Check Tags: Animal; Female; Support, Non-U.S. Gov't
*1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
Behavior, Animal: DE, drug effects
Disease Models, Animal
Dizocilpine Maleate: PD, pharmacology
*Dopamine Agents: PD, pharmacology
Dose-Response Relationship, Drug
Drug Interactions
Locomotion: DE, drug effects
Macaca nemestrina
Motor Activity: DE, drug effects
Parkinson Disease, Secondary: CI, chemically induced
***Parkinson Disease, Secondary: DT, drug therapy**
Parkinson Disease, Secondary: PP, physiopathology
*Receptors, Dopamine D1: PH, physiology
*Receptors, Dopamine D2: PH, physiology
*Receptors, N-Methyl-D-Aspartate: AI, antagonists & inhibitors
Variation (Genetics): PH, physiology
RN 28289-54-5 (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine); 77086-22-7 (Dizocilpine Maleate)
CN 0 (Dopamine Agents); 0 (Receptors, Dopamine D1); 0 (Receptors, Dopamine D2); 0 (Receptors, N-Methyl-D-Aspartate)

L97 ANSWER 41 OF 44 MEDLINE
AN 93128009 MEDLINE
DN 93128009 PubMed ID: 8093574
TI The effects of D1 and D2 dopamine receptor agonist and antagonist on parkinsonism in chronic MPTP-treated monkeys.
AU Nomoto M; Fukuda T
CS Department of Pharmacology, Kagoshima University, Japan.
SO ADVANCES IN NEUROLOGY, **(1993)** 60 119-22.
Journal code: 0367524. ISSN: 0091-3952.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199302
ED Entered STN: 19930226
Last Updated on STN: 20000303
Entered Medline: 19930211
CT Check Tags: Animal; Female; Male; Support, Non-U.S. Gov't
*1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine: PD, pharmacology
*Antiparkinson Agents: PD, pharmacology
Callithrix
Corpus Striatum: DE, drug effects
Corpus Striatum: PP, physiopathology
Dopamine: PH, physiology
*Dopamine Agents: PD, pharmacology
Dose-Response Relationship, Drug
Indoles: PD, pharmacology
Motor Activity: DE, drug effects
Motor Activity: PH, physiology
***Parkinson Disease, Secondary: CI, chemically induced**
Parkinson Disease, Secondary: PP, physiopathology
Phenanthridines: PD, pharmacology
Receptors, Dopamine D1: AI, antagonists & inhibitors
*Receptors, Dopamine D1: DE, drug effects
Receptors, Dopamine D1: PH, physiology
Receptors, Dopamine D2: AI, antagonists & inhibitors
*Receptors, Dopamine D2: DE, drug effects
Receptors, Dopamine D2: PH, physiology
Sch-23390: PD, pharmacology
RN 100999-26-6 (CY 208-243); 28289-54-5 (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine); 51-61-6 (Dopamine); **80751-65-1 (SK&F 82958)** ; 87075-17-0 (Sch-23390)
CN 0 (Antiparkinson Agents); 0 (Dopamine Agents); 0 (Indoles); 0 (Phenanthridines); 0 (Receptors, Dopamine D1); 0 (Receptors, Dopamine D2)

L97 ANSWER 42 OF 44 MEDLINE
AN 92386526 MEDLINE
DN 92386526 PubMed ID: 1355407
TI Weak antiparkinsonian activity of the D1 agonist C-APB (**SKF 82958**) and lack of synergism with a D2 agonist in primates.
AU Rupniak N M; Boyce S; Steventon M; Iversen S D
CS Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Harlow, Essex, U.K.
SO CLINICAL NEUROPHARMACOLOGY, **(1992 Aug)** 15 (4) 307-9.
Journal code: 7607910. ISSN: 0362-5664.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199210
ED Entered STN: 19921023
Last Updated on STN: 20000303

Entered Medline: 19921006

AB The role of D1 receptors in motor control is poorly understood. In parkinsonian squirrel monkeys, the full D1 agonist C-APB (**SKF 82958**; 0.1-0.4 mg/kg s.c.) caused weak stimulation of locomotor activity. However, the motor stimulant effects of the D2 agonist (+)-PHNO (0.001 mg/kg s.c.) were not potentiated by C-APB (0.3 mg/kg). Differences between these observations and expectations from experiments using rodents are discussed.

CT Check Tags: Animal; Male
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
*Antiparkinson Agents: PD, pharmacology
*Dopamine Agents: PD, pharmacology
Drug Synergism
Motor Activity: DE, drug effects
Parkinson Disease, Secondary: CI, chemically induced
Parkinson Disease, Secondary: PP, physiopathology
*Receptors, Dopamine: PH, physiology
Receptors, Dopamine D1
Receptors, Dopamine D2
Saimiri

RN 28289-54-5 (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine); **80751-65-1 (SK&F 82958)**

CN 0 (Antiparkinson Agents); 0 (Dopamine Agents); 0 (Receptors, Dopamine); 0 (Receptors, Dopamine D1); 0 (Receptors, Dopamine D2)

L97 ANSWER 43 OF 44 MEDLINE

AN 92079697 MEDLINE

DN 92079697 PubMed ID: 1836030

TI The D1 receptor antagonist, SCH 23390, induces signs of parkinsonism in African green monkeys.

AU Lawrence M S; Redmond D E Jr; Elsworth J D; Taylor J R; Roth R H

CS Neurobehavior Laboratory, Yale University School of Medicine, New Haven, Ct. 06510.

NC MH00643 (NIMH)
MH14092 (NIMH)
NS24032 (NINDS)

SO LIFE SCIENCES, **(1991)** 49 (25) PL229-34.
Journal code: 0375521. ISSN: 0024-3205.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199201

ED Entered STN: 19920202
Last Updated on STN: 20000303
Entered Medline: 19920113

AB Systemic administration of the selective D1 antagonist, SCH 23390, caused significant motor changes in healthy African green monkeys. The effects included the parkinsonian signs of motor freezing, incoordination, bradykinesia, poverty of movement, tremor and depressed blink rate. SCH 23390 administered to MPTP-treated monkeys increased existing parkinsonism. The results are of particular interest in light of recent data that demonstrate the effectiveness of **dihydrexidine**, a full D1 agonist, in alleviating parkinsonism in MPTP-treated monkeys. These data implicate D1 receptors in the functions impaired by Parkinson's disease and suggest the possibility of parkinsonian side effects in the clinical use of this or similar D1 antagonists as treatments for psychiatric disorders.

CT Check Tags: Animal; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Analysis of Variance
Behavior, Animal: DE, drug effects
Blinking: DE, drug effects

Cercopithecus aethiops
*Dopamine Antagonists
***Parkinson Disease, Secondary: CI, chemically induced**
Parkinson Disease, Secondary: PP, physiopathology
Receptors, Dopamine: PH, physiology
Receptors, Dopamine D1
*Sch-23390: PD, pharmacology
RN 87075-17-0 (Sch-23390)
CN 0 (Dopamine Antagonists); 0 (Receptors, Dopamine); 0 (Receptors, Dopamine D1)

L97 ANSWER 44 OF 44 MEDLINE
AN 92008246 MEDLINE
DN 92008246 PubMed ID: 1680717
TI **Dihydrexidine**, a full dopamine D1 agonist, reduces MPTP-induced parkinsonism in monkeys.
AU Taylor J R; Lawrence M S; Redmond D E Jr; Elsworth J D; Roth R H; Nichols D E; Mailman R B
CS Department of Psychiatry, Yale University School of Medicine, New Haven, CT 06510.
NC MH40537 (NIMH)
MH42705 (NIMH)
NS24032 (NINDS)
+
SO EUROPEAN JOURNAL OF PHARMACOLOGY, **(1991 Jul 9)** 199 (3) 389-91.
Journal code: 1254354. ISSN: 0014-2999.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199111
ED Entered STN: 19920124
Last Updated on STN: 20000303
Entered Medline: 19911115
CT Check Tags: Animal; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
*1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
Cercopithecus aethiops
Dopamine: PH, physiology
*Dopamine Agents: PD, pharmacology
Parkinson Disease, Secondary: CI, chemically induced
***Parkinson Disease, Secondary: DT, drug therapy**
*Phenanthridines: PD, pharmacology
RN **123039-93-0 (dihydrexidine)**; 28289-54-5 (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine); 51-61-6 (Dopamine)
CN 0 (Dopamine Agents); 0 (Phenanthridines)

=> fil reg
FILE 'REGISTRY' ENTERED AT 14:32:16 ON 24 JUN 2003

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 23 JUN 2003 HIGHEST RN 536496-82-9
DICTIONARY FILE UPDATES: 23 JUN 2003 HIGHEST RN 536496-82-9

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

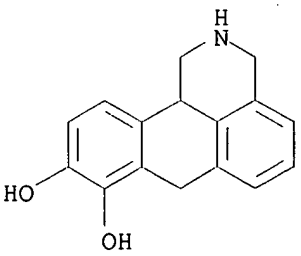
Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d ide can l29 tot

L29 ANSWER 1 OF 22 REGISTRY COPYRIGHT 2003 ACS
RN 400786-40-5 REGISTRY
CN 1H-Dibenz[de,h]isoquinoline-8,9-diol, 2,3,7,11b-tetrahydro-, hydrobromide (4:5) (9CI) (CA INDEX NAME)
MF C16 H15 N O2 . 5/4 Br H
SR CA
LC STN Files: CA, CAPLUS, CASREACT
CRN (221032-27-5)



Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
CM1 1E07 – 703-308-4498
jan.delaval@uspto.gov

●5/4 HBr

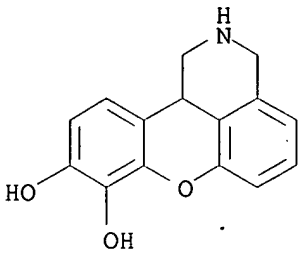
2 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1: 137:232533

REFERENCE 2: 136:200115

L29 ANSWER 2 OF 22 REGISTRY COPYRIGHT 2003 ACS
RN 313484-61-6 REGISTRY
CN [1]Benzopyrano[4,3,2-de]isoquinoline-8,9-diol, 1,2,3,11b-tetrahydro-, hydrobromide (9CI) (CA INDEX NAME)
OTHER NAMES:

CN **Dinoxyline**
MF C15 H13 N O3 . Br H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



● HBr

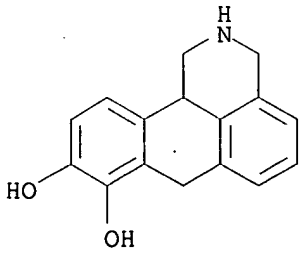
3 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1: 137:279051

REFERENCE 2: 137:103908

REFERENCE 3: 134:56658

L29 ANSWER 3 OF 22 REGISTRY COPYRIGHT 2003 ACS
RN 221032-27-5 REGISTRY
CN 1H-Dibenz[de,h]isoquinoline-8,9-diol, 2,3,7,11b-tetrahydro- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Dinapsoline**
FS 3D CONCORD
MF C16 H15 N O2
CI COM
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, CASREACT, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

6 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
6 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1: 137:279051

REFERENCE 2: 137:232533

REFERENCE 3: 137:103908

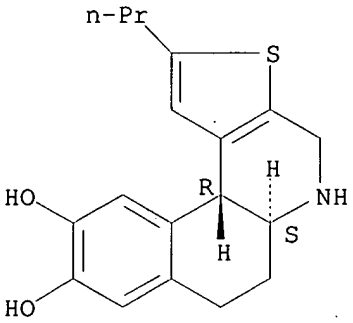
REFERENCE 4: 134:340412

REFERENCE 5: 134:125884

REFERENCE 6: 130:223157

L29 ANSWER 4 OF 22 REGISTRY COPYRIGHT 2003 ACS
RN 190076-78-9 REGISTRY
CN Benzo[f]thieno[2,3-c]quinoline-9,10-diol, 4,5,5a,6,7,11b-hexahydro-2-propyl-, hydrobromide, (5aS-trans)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C18 H21 N O2 S . Br H
SR CA
LC STN Files: CA, CAPLUS
CRN (171961-96-9)

Absolute stereochemistry.



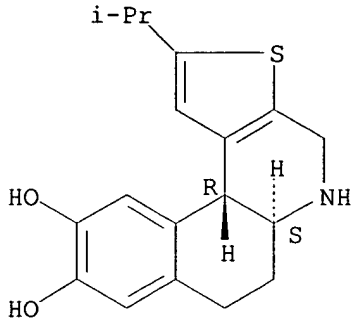
● HBr

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1: 127:5027

L29 ANSWER 5 OF 22 REGISTRY COPYRIGHT 2003 ACS
RN 187661-45-6 REGISTRY
CN Benzo[f]thieno[2,3-c]quinoline-9,10-diol, 4,5,5a,6,7,11b-hexahydro-2-(1-methylethyl)-, trans- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF **C18 H21 N O2 S**
CI COM
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Relative stereochemistry.



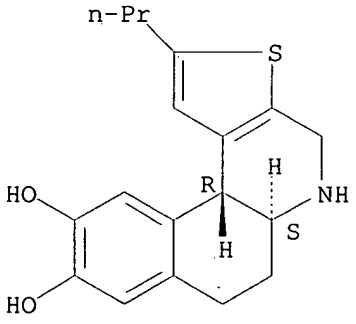
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1: 126:199569

L29 ANSWER 6 OF 22 REGISTRY COPYRIGHT 2003 ACS
RN **187661-43-4** REGISTRY
CN Benzo[f]thieno[2,3-c]quinoline-9,10-diol, 4,5,5a,6,7,11b-hexahydro-2-propyl-, (5aR,11bS)-rel- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Benzo[f]thieno[2,3-c]quinoline-9,10-diol, 4,5,5a,6,7,11b-hexahydro-2-propyl-, trans-
FS STEREOSEARCH
MF C18 H21 N O2 S
CI COM
SR CA
LC STN Files: CA, CAPLUS, DRUGUPDATES, USPATFULL

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

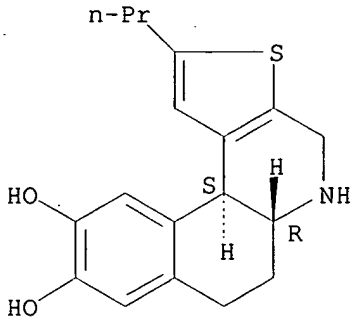
REFERENCE 1: 135:335185

REFERENCE 2: 126:199569

L29 ANSWER 7 OF 22 REGISTRY COPYRIGHT 2003 ACS
RN 178357-34-1 REGISTRY
CN Benzo[f]thieno[2,3-c]quinoline-9,10-diol, 4,5,5a,6,7,11b-hexahydro-2-

propyl-, hydrobromide, (5aR-trans)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
DR 166590-80-3
MF C18 H21 N O2 S . Br H
SR CA
LC STN Files: CA, CAPLUS, CASREACT, USPATFULL
CRN (171961-95-8)

Absolute stereochemistry. Rotation (-).



● HBr

5 REFERENCES IN FILE CA (1957 TO DATE)
5 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1: 127:248092

REFERENCE 2: 126:277416

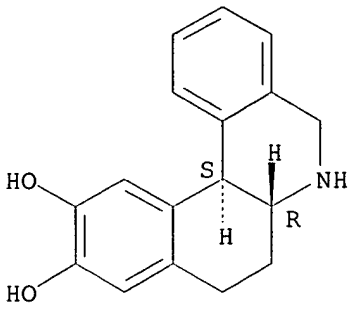
REFERENCE 3: 126:199569

REFERENCE 4: 125:58329

REFERENCE 5: 123:143898

L29 ANSWER 8 OF 22 REGISTRY COPYRIGHT 2003 ACS
RN 174691-84-0 REGISTRY
CN Benzo[a]phenanthridine-10,11-diol, 5,6,6a,7,8,12b-hexahydro-, (6aR-trans)-(9CI) (CA INDEX NAME)
OTHER NAMES:
CN (+)-Dihydrexidine
FS STEREOSEARCH
MF **C17 H17 N O2**
CI COM
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry. Rotation (+).



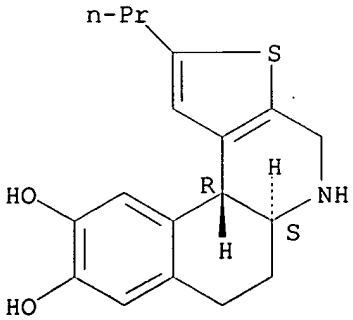
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1: 124:212058

L29 ANSWER 9 OF 22 REGISTRY COPYRIGHT 2003 ACS
RN 173934-91-3 REGISTRY
CN Benzo[f]thieno[2,3-c]quinoline-9,10-diol, 4,5,5a,6,7,11b-hexahydro-2-propyl-, hydrochloride, (5aR,11bS)-rel- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Benzo[f]thieno[2,3-c]quinoline-9,10-diol, 4,5,5a,6,7,11b-hexahydro-2-propyl-, hydrochloride, trans-
OTHER NAMES:
CN **A 86929**
CN A 86929.1
FS STEREOSEARCH
MF C18 H21 N O2 S . Cl H
SR CA
LC STN Files: ADISINSIGHT, CA, CAPLUS, DRUGNL, DRUGUPDATES, EMBASE, TOXCENTER, USPATFULL
CRN (187661-43-4)

Relative stereochemistry.



HCl

15 REFERENCES IN FILE CA (1957 TO DATE)
15 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1: 138:309049

REFERENCE 2: 137:333164

REFERENCE 3: 137:118860

REFERENCE 4: 135:335185

REFERENCE 5: 133:12675

REFERENCE 6: 131:102216

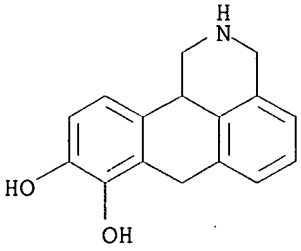
REFERENCE 7: 131:82910

REFERENCE 8: 131:609

REFERENCE 9: 130:262135

REFERENCE 10: 130:46932

L29 ANSWER 10 OF 22 REGISTRY COPYRIGHT 2003 ACS
RN 173548-62-4 REGISTRY
CN 1H-Dibenz[de,h]isoquinoline-8,9-diol, 2,3,7,11b-tetrahydro-, hydrobromide (9CI) (CA INDEX NAME)
MF C16 H15 N O2 . Br H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (221032-27-5)



● HBr

4 REFERENCES IN FILE CA (1957 TO DATE)
4 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1: 138:187648

REFERENCE 2: 129:170879

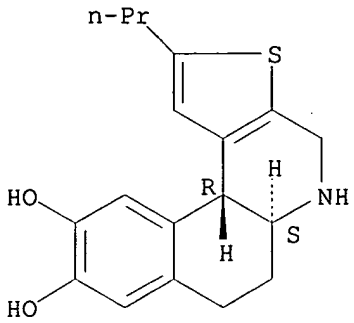
REFERENCE 3: 126:238315

REFERENCE 4: 124:145875

L29 ANSWER 11 OF 22 REGISTRY COPYRIGHT 2003 ACS
RN 171961-96-9 REGISTRY
CN Benzo[f]thieno[2,3-c]quinoline-9,10-diol, 4,5,5a,6,7,11b-hexahydro-2-propyl-, (5aS-trans)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF **C18 H21 N O2 S**

CI COM
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



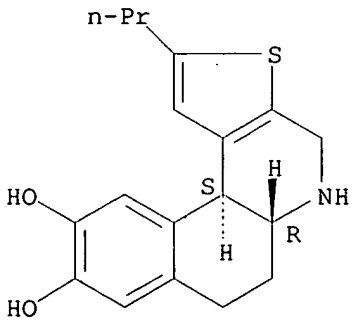
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1: 124:145940

L29 ANSWER 12 OF 22 REGISTRY COPYRIGHT 2003 ACS
RN 171961-95-8 REGISTRY
CN Benzo[f]thieno[2,3-c]quinoline-9,10-diol, 4,5,5a,6,7,11b-hexahydro-2-propyl-, (5aR-trans)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
DR 187661-58-1
MF **C18 H21 N O2 S**
CI COM
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

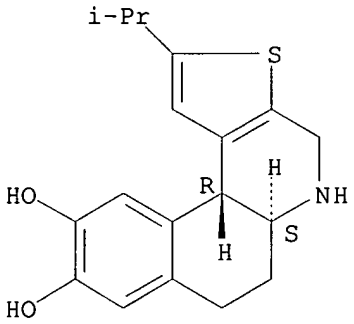
2 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1: 126:199569

REFERENCE 2: 124:145940

L29 ANSWER 13 OF 22 REGISTRY COPYRIGHT 2003 ACS
RN 166590-67-6 REGISTRY
CN Benzo[f]thieno[2,3-c]quinoline-9,10-diol, 4,5,5a,6,7,11b-hexahydro-2-(1-methylethyl)-, hydrobromide, trans- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C18 H21 N O2 S . Br H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (187661-45-6)

Relative stereochemistry.



● HBr

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

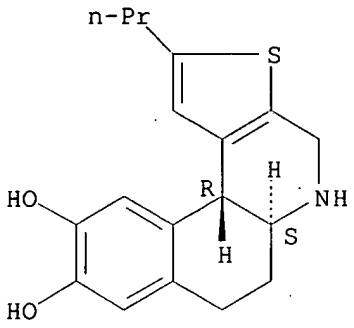
REFERENCE 1: 127:5027

REFERENCE 2: 126:199569

REFERENCE 3: 123:143898

L29 ANSWER 14 OF 22 REGISTRY COPYRIGHT 2003 ACS
RN 166590-65-4 REGISTRY
CN Benzo[f]thieno[2,3-c]quinoline-9,10-diol, 4,5,5a,6,7,11b-hexahydro-2-propyl-, hydrobromide, trans- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C18 H21 N O2 S . Br H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (187661-43-4)

Relative stereochemistry.



● HBr

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

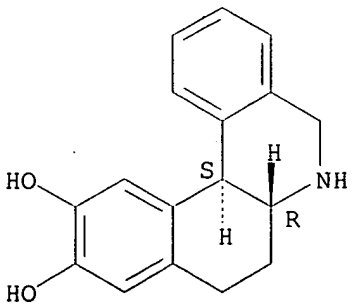
REFERENCE 1: 127:5027

REFERENCE 2: 126:199569

REFERENCE 3: 123:143898

L29 ANSWER 15 OF 22 REGISTRY COPYRIGHT 2003 ACS
RN 158704-02-0 REGISTRY
CN Benzo[a]phenanthridine-10,11-diol, 5,6,6a,7,8,12b-hexahydro-, hydrochloride, (6aR,12bS)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Benzo[a]phenanthridine-10,11-diol, 5,6,6a,7,8,12b-hexahydro-, hydrochloride, (6aR-trans)-
FS STEREOSEARCH
MF C17 H17 N O2 . Cl H
SR CA
LC STN Files: CA, CAPLUS
CRN (174691-84-0)

Absolute stereochemistry. Rotation (+).



HCl

4 REFERENCES IN FILE CA (1957 TO DATE)
4 REFERENCES IN FILE CAPLUS (1957 TO DATE)

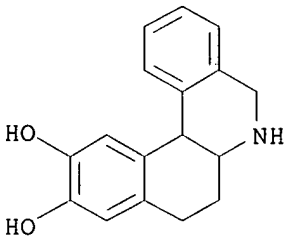
REFERENCE 1: 136:279312

REFERENCE 2: 125:10634

REFERENCE 3: 123:74809

REFERENCE 4: 121:245104

L29 ANSWER 16 OF 22 REGISTRY COPYRIGHT 2003 ACS
RN 150811-05-5 REGISTRY
CN Benzo[a]phenanthridine-10,11-diol, 5,6,6a,7,8,12b-hexahydro- (9CI) (CA INDEX NAME)
MF **C17 H17 N O2**
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS
(*File contains numerically searchable property data)



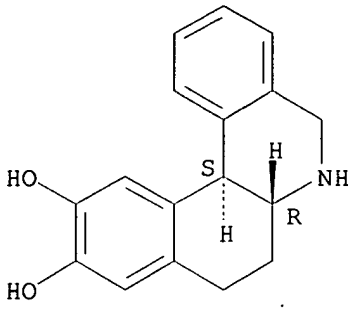
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1: 119:217619

L29 ANSWER 17 OF 22 REGISTRY COPYRIGHT 2003 ACS
RN 137417-08-4 REGISTRY
CN Benzo[a]phenanthridine-10,11-diol, 5,6,6a,7,8,12b-hexahydro-, hydrochloride, trans- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
DR 126327-49-9
MF C17 H17 N O2 . Cl H
SR CA
LC STN Files: ADISINSIGHT, BEILSTEIN*, CA, CAPLUS, CHEMCATS, USPATFULL
(*File contains numerically searchable property data)
CRN (123039-93-0)

Relative stereochemistry.



● HCl

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

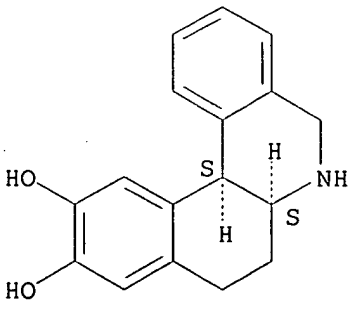
REFERENCE 1: 122:282073

REFERENCE 2: 115:256024

REFERENCE 3: 112:235152

L29 ANSWER 18 OF 22 REGISTRY COPYRIGHT 2003 ACS
RN 126295-97-4 REGISTRY
CN Benzo[a]phenanthridine-10,11-diol, 5,6,6a,7,8,12b-hexahydro-, hydrobromide, cis- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Benzo[a]phenanthridine-10,11-diol, 5,6,6a,7,8,12b-hexahydro-, hydrobromide, cis-(.+-.)-
FS STEREOSEARCH
MF C17 H17 N O2 . Br H
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT
(*File contains numerically searchable property data)
CRN (123385-19-3)

Relative stereochemistry.



HBr

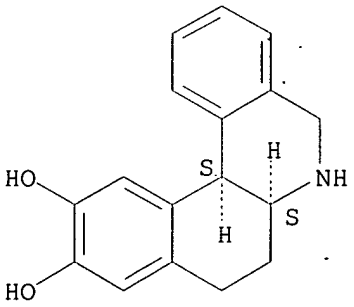
1 REFERENCES IN FILE CA (1957 TO DATE)

1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1: 112:235152

L29 ANSWER 19 OF 22 REGISTRY COPYRIGHT 2003 ACS
RN 123385-19-3 REGISTRY
CN Benzo[a]phenanthridine-10,11-diol, 5,6,6a,7,8,12b-hexahydro-, cis- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN cis-Dihydrexidine
FS STEREOSEARCH
DR 126295-96-3
MF **C17 H17 N O2**
CI COM
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, DRUGUPDATES
(*File contains numerically searchable property data)

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

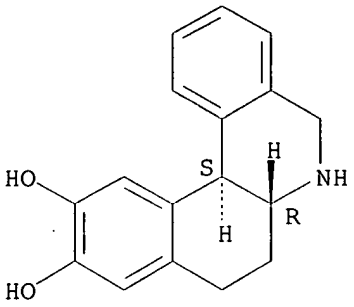
REFERENCE 1: 124:25747

REFERENCE 2: 112:235152

REFERENCE 3: 111:187294

L29 ANSWER 20 OF 22 REGISTRY COPYRIGHT 2003 ACS
RN 123039-93-0 REGISTRY
CN Benzo[a]phenanthridine-10,11-diol, 5,6,6a,7,8,12b-hexahydro-, (6aR,12bS)-rel- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Benzo[a]phenanthridine-10,11-diol, 5,6,6a,7,8,12b-hexahydro-, trans-
OTHER NAMES:
CN **Dihydrexidine**
FS STEREOSEARCH
DR 126295-91-8
MF **C17 H17 N O2**
CI COM
SR CA
LC STN Files: ADISINSIGHT, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CIN, CSCHEM, DRUGNL, DRUGUPDATES, EMBASE, MEDLINE, PHAR, PROMT, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

61 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
61 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1: 138:379244

REFERENCE 2: 138:297427

REFERENCE 3: 138:248855

REFERENCE 4: 137:362974

REFERENCE 5: 137:362973

REFERENCE 6: 137:279051

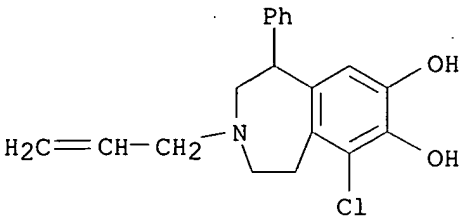
REFERENCE 7: 137:103908

REFERENCE 8: 136:395908

REFERENCE 9: 136:129077

REFERENCE 10: 134:277290

L29 ANSWER 21 OF 22 REGISTRY COPYRIGHT 2003 ACS
RN 80751-65-1 REGISTRY
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (.+-.)-SKF 82958
CN **SKF 82958**
FS 3D CONCORD
DR 148440-82-8
MF C19 H20 Cl N O2
CI COM
LC STN Files: ADISINSIGHT, AGRICOLA, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CHEMCATS, DDFU, DRUGU, EMBASE, MEDLINE, TOXCENTER, USPATFULL, VETU
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

166 REFERENCES IN FILE CA (1957 TO DATE)
168 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1: 138:396546

REFERENCE 2: 138:379244

REFERENCE 3: 138:297529

REFERENCE 4: 138:198652

REFERENCE 5: 138:166825

REFERENCE 6: 138:147522

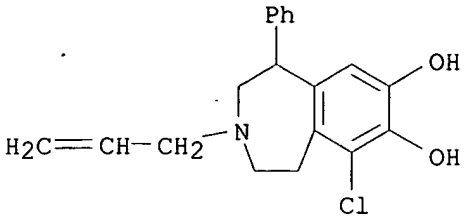
REFERENCE 7: 137:333164

REFERENCE 8: 137:211238

REFERENCE 9: 137:164002

REFERENCE 10: 137:134940

L29 ANSWER 22 OF 22 REGISTRY COPYRIGHT 2003 ACS
RN 74115-01-8 REGISTRY
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)-, hydrobromide (9CI) (CA INDEX NAME)
OTHER NAMES:
CN SKF 82598
DR 163087-29-4
MF C19 H20 Cl N O2 . Br H
LC STN Files: BEILSTEIN*, CA, CAPLUS, CHEMCATS, RTECS*, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)
CRN (80751-65-1)



● HBr

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

15 REFERENCES IN FILE CA (1957 TO DATE)
15 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1: 137:346676

REFERENCE 2: 137:180090

REFERENCE 3: 136:129077

REFERENCE 4: 133:278952

REFERENCE 5: 131:332460

REFERENCE 6: 131:125291

REFERENCE 7: 130:262135

REFERENCE 8: 128:71079

REFERENCE 9: 125:79715

REFERENCE 10: 124:45533

=> d his

FILE 'REGISTRY' ENTERED AT 13:44:49 ON 24 JUN 2003
E A 86929/CN
L1 1 S E3
L2 1 S 187661-43-4
E C18H21NO2S/MF
L3 12 S E3 AND SC4-NC5-C6-C6/ES
L4 4 S L3 NOT DIOL
L5 8 S L3 NOT L4
L6 4 S L5 NOT 2 PROPYL
L7 2 S L6 NOT 3 PROPYL
L8 1 S L7 NOT 166590-94-9
L9 2 S L2,L8
L10 3 S L5 NOT L6-L9
L11 2 S L10 NOT 187661-53-6
L12 4 S L9,L11,L2
L13 8 S L3 NOT L12
SEL RN L12
L14 5 S E1-E4/CRN

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L15           9 S L1,L2,L12,L14
                E SKF 82958/CN
L16           1 S E3
                SEL RN
L17           1 S E1/CRN
L18           2 S L16,L17
                E DINAPSOLINE/CN
L19           1 S E3
                E DINOXYLINE/CN
L20           1 S E3
                E DIHYDREXIDINE/CN
L21           1 S E3
                E C17H17NO2/MF
L22          35 S E3 AND NC5-C6-C6-C6/ES
L23          23 S L22 NOT 10 11 DIOL
L24          12 S L22 NOT L23
L25           4 S L24 NOT (6 METHYL OR (D OR T)/ELS)
L26           6 S L19-L21,L25
                SEL RN
L27           5 S E1-E6/CRN
L28          11 S L26,L27
L29          22 S L15,L18,L28

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L30         262 S L29
L31         325 S A86929 OR A()(86929 OR 86 929) OR SKF82958 OR SKF()(82958 OR
L32         357 S L30,L31
                E PARKINSON/CT
L33       10057 S E6-E15
                E E6+ALL
L34       10013 S E4,E3+NT
                E E9+ALL
L35        2556 S E4
                E E12+ALL
                E E10+ALL
L36         938 S E3
L37          70 S L32 AND L33-L36
L38          84 S L32 AND ?PARKINSON?
L39          84 S L37,L38
                E NICHOLS D/AU
L40         285 S E3,E11,E32,E36,E37
                E MAILMAN R/AU
L41         181 S E3-E7
                E HUANG X/AU
L42         956 S E3-E27
                E HUANG XUE/AU
L43          11 S E3,E14
L44          44 S E59
L45          43 S L32 AND L40-L44
L46          11 S L39 AND L45
L47           4 S (US5597832 OR US5659037 OR US5668141)/PN
                SEL RN

     FILE 'REGISTRY' ENTERED AT 14:15:09 ON 24 JUN 2003
L48         313 S E627-E939

     FILE 'HCAPLUS' ENTERED AT 14:15:49 ON 24 JUN 2003
L49           4 S L48/P AND L47
                SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 14:16:10 ON 24 JUN 2003
L50         250 S E1-E250
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L51          223 S L50
L52            8 S L51 AND L33-L36
L53            9 S L51 AND ?PARKINSON?
L54           20 S L52,L53,L46
L55           18 S L39 AND L54
L56           20 S L54,L55
L57           66 S L39 NOT L56
L58           61 S L29(L)THU/RL
L59            9 S L58 AND L56
L60           11 S L56 NOT L59
L61           20 S L59,L60
L62           52 S L58 NOT L59-L61
L63           20 S L61 AND L30-L47,L49,L51-L62
L64           52 S L62 AND L30-L47,L59,L51-L63
L65           30 S L64 AND (PARKINSON? OR ANTIPARKINSON?)/CW
L66           22 S L64 NOT L65
L67           50 S L63,L65
L68            4 S L66 AND L45
L69           54 S L67,L68
L70           64 S L39,L45 NOT L69
L71            1 S L58 AND L70
L72           51 S L67,L71
L73           28 S L70 AND L45
L74           64 S L70,L73
L75           72 S L61-L74 AND (PARKINSON? OR ANTIPARKINSON?)/CW
L76           63 S L61-L74 NOT L75
L77           14 S L76 AND (PARKINSON? OR ANTIPARKINSON?)/AB,TI
L78           86 S L75,L77
L79           49 S L76 NOT L78
L80           73 S L78 AND (PY<=2000 OR PRY<=2000 OR AY<=2000)
L81           62 S L80 AND L30
L82           11 S L80 NOT L81
L83            1 S L82 AND MAILMAN ?/AU
L84           63 S L81,L83
L85           13 S L78 NOT L80-L84
L86            3 S L85 AND NICHOLS ?/AU
L87           66 S L84,L86

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=> fil hcaplus
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USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)
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FILE COVERS 1907 - 24 Jun 2003  VOL 138 ISS 26
FILE LAST UPDATED: 23 Jun 2003  (20030623/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.
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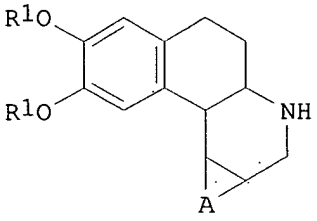
=> d l49 bib abs hitrn fhitstr tot

L49 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2003 ACS
AN 1997:617009 HCAPLUS
DN 127:293207
TI Trans-2,6-,3,6-and 4,6-diaza-5,6,6a,7,8,12b-hexahydrobenzo[c]phenanthrene compounds as dopamine agonists
IN Shiosaki, Kazumi; Gu, Yu Gui; Michaelides, Michael
PA Abbott Laboratories, USA
SO U.S., 20 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 5668141	A	19970916	US 1996-626654	19960402 <--
WO 9736902	A1	19971009	WO 1997-US5069	19970321

W: CA, JP, MX
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRAI US 1996-626654 19960402
OS MARPAT 127:293207
GI



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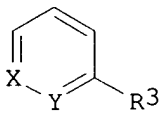
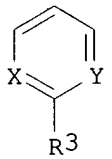


II


III

These are the patents cited in claims, page 8 all these cmpds were used in search

AB Tetracyclic compds. I [A and the atoms to which it is attached comprise a pyridine ring selected from II or III; R1 = H, cleavable group; one of X and Y is N and the other is CR2; R2, R3 = H, halo, alkyl, alkoxy, haloalkyl; one of R2 and R3 = cycloalkyl; R2R3 = cycloalkene] were prepd. and their dopamine agonist activity detd. E.g., to a soln. of picolinic acid was added pivaloyl chloride/NEt3, then Me3CNH2, to give picolinic acid tert-butylamide. The last was treated with BuLi, and 1,2-dihydro-6,7-dimethoxy-3-nitronaphthalene added to give trans-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(2-tert-butylcarboxamido-3-pyridyl)-2-nitronaphthalene. Redn. of the nitro deriv., followed by cyclization and deprotection, gave trans-4,6-diaza-5,6,6a,7,8,12b-hexahydrobenzo[c]phenanthrene-10,11-diol dihydrobromide. The title compds. had high activity as dopamine agonists.

IT **197007-49-1P 197007-51-5P 197007-53-7P**
197007-55-9P 197007-60-6P 197007-63-9P
197007-65-1P 197007-67-3P 197007-69-5P
197007-71-9P 197007-73-1P 197007-77-5P
197007-79-7P 197007-97-9P 197007-98-0P
197007-99-1P 197008-00-7P 197008-01-8P
197008-02-9P 197008-03-0P 197008-04-1P
197008-05-2P 197008-06-3P 197008-07-4P
197008-08-5P 197008-09-6P 197008-10-9P
197008-11-0P 197008-12-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);

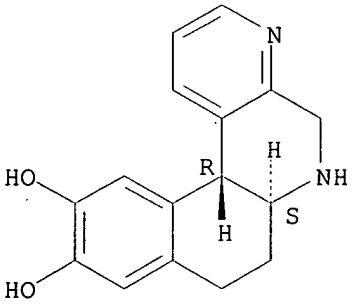
BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of diazahexahydrobenzophenanthrenes as dopamine agonists)

IT **71653-50-4P 177273-32-4P 197007-85-5P**
197007-86-6P 197007-87-7P 197007-88-8P
197007-89-9P 197007-90-2P 197007-91-3P
197007-92-4P 197007-93-5P 197007-94-6P
197007-95-7P 197007-96-8P 197008-13-2P
197008-14-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of diazahexahydrobenzophenanthrenes as dopamine agonists)

IT **197007-49-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of diazahexahydrobenzophenanthrenes as dopamine agonists)

RN 197007-49-1 HCAPLUS
CN Naphtho[1,2-f][1,7]naphthyridine-10,11-diol, 5,6,6a,7,8,12b-hexahydro-, dihydrobromide, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



●2 HBr

L49 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2003 ACS
AN 1997:574535 HCAPLUS
DN 127:248092
TI Process for preparing chiral tetracyclic dopaminergic compounds
IN Ehrlich, Paul P.; Michaelides, Michael R.; Mclaughlin, Maureen A.; Hsaio, Chi-nung
PA Abbott Laboratories, USA
SO U.S., 10 pp., Cont.-in-part of U.S. Ser. No. 292,677.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	US 5659037	A	19970819	US 1995-463326	19950605	<--
	CA 2195676	AA	19960229	CA 1995-2195676	19950803	
	WO 9606085	A1	19960229	WO 1995-US9859	19950803	
	W: CA, JP, MX					
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
	EP 777655	A1	19970611	EP 1995-927566	19950803	
	EP 777655	B1	20010110			
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE					
	JP 10504564	T2	19980506	JP 1995-508096	19950803	

	AT 198592	E	20010115	AT 1995-927566	19950803
	ES 2155893	T3	20010601	ES 1995-927566	19950803
PRAI	US 1994-292677	A2	19940818		
	US 1995-463326	A	19950605		
	WO 1995-US9859	W	19950803		

OS MARPAT 127:248092

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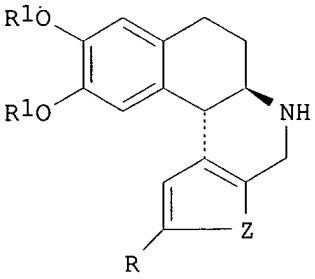

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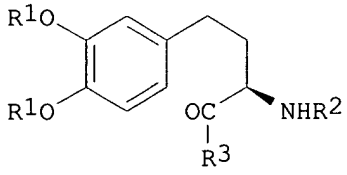


II

AB Azacyclopentaphenanthrenes I [R = alkyl; R1 = H; Z = O, S, CH:CH] were prepd. by amidating an acid II [R1, R2 = protective group; R3 = OH] with MeNHOMe in presence of N-methylmorpholine and iso-Bu chloroformate, reaction of the amide with a furan, thiophene, or benzene deriv., redn. of the keto group to the alc., cyclization to the naphthalene deriv., and closure of the N-contg. ring. Thus, I [R = Pr, R1 = H, Z = S] was obtained from (R)-3,4-(MeO)C6H3COCH2CH(NHCOCF3)CO2H in 10 steps and 48% overall yield.

IT **178357-34-1P 178357-35-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(stereoselective prepn. of thiaazacyclopentaphenanthrenediol)

IT **36155-78-9P**, 4-Bromo-2-propionylthiophene **36155-79-0P**, 4-Bromo-2-propylthiophene **97403-64-0P 97403-65-1P 178201-91-7P 178201-92-8P 178201-94-0P 178201-95-1P 178201-96-2P 178201-97-3P 178201-98-4P 178357-37-4P 178357-38-5P 195259-61-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(stereoselective prepn. of thiaazacyclopentaphenanthrenediol)

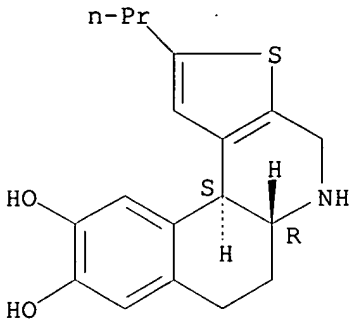
IT **171482-82-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(stereoselective prepn. of thiaazacyclopentaphenanthrenediol)

IT **178357-34-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(stereoselective prepn. of thiaazacyclopentaphenanthrenediol)

RN 178357-34-1 HCAPLUS

CN Benzo[f]thieno[2,3-c]quinoline-9,10-diol, 4,5,5a,6,7,11b-hexahydro-2-propyl-, hydrobromide, (5aR-trans)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● HBr

L49 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2003 ACS
AN 1997:102096 HCAPLUS
DN 126:199569
TI Tetracyclic compounds as dopamine agonists
IN Michaelides, Michael R.; Hong, Yufeng
PA Abbott Laboratories, USA
SO U.S., 38 pp., Cont.-in-part of U.S. Ser. No. 209,982, abandoned.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5597832	A	19970128	US 1994-337348	19941110 <--
	IL 108993	A1	20000831	IL 1994-108993	19940316
	CA 2159481	AA	19941013	CA 1994-2159481	19940318
	CN 1124489	A	19960612	CN 1994-192241	19940318
	CN 1046723	B	19991124		
PRAI	US 1993-43424	B2	19930406		
	US 1994-209982	B2	19940317		

OS MARPAT 126:199569
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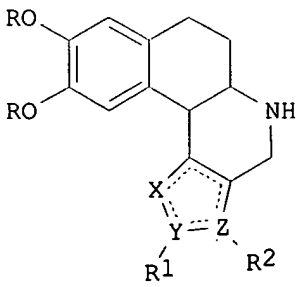

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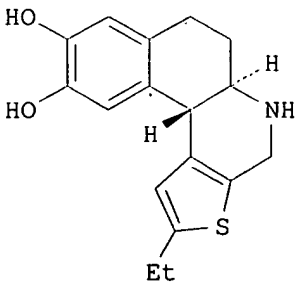

II

AB Tetracyclic compds. I [R = H, prodrug moiety; R1 = H, alkyl, CF3, cycloalkyl, Ph, thienyl; R2 = H, alkyl, CF3, Cl, cycloalkyl; X, Z = C, N, O, S; Y = C, O, S] are prepd. as dopamine agonists. Thus, the thiaazacyclopentaphenanthrene compd. II.HBr is prepd. from 2-ethylthiophene and 1,2-dihydro-6,7-dimethoxy-3-nitronaphthalene in 8 steps. The competitive binding data (Ki values) from the D-1 and D-2

receptor binding assays for II.HBr are 0.006 and 0.64 .mu.M resp.

IT **166590-61-0P 166590-62-1P 166590-63-2P**
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166590-67-6P 166590-68-7P 166590-70-1P
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166590-81-4P 166590-82-5P 166590-83-6P
166590-84-7P 166590-85-8P 166590-90-5P
166590-92-7P 166590-93-8P 166590-94-9P
166590-95-0P 166590-96-1P 166590-97-2P
166590-98-3P 166590-99-4P 166591-00-0P
166591-01-1P 166591-02-2P 166591-03-3P
166591-04-4P 166591-05-5P 166591-06-6P
166591-11-3P 166591-27-1P 171752-56-0P
171961-95-8P 178357-34-1P 187660-85-1P
187660-86-2P 187660-87-3P 187660-88-4P
187660-89-5P 187660-92-0P 187660-93-1P
187660-94-2P 187660-95-3P 187660-96-4P
187660-97-5P 187660-98-6P 187661-40-1P
187661-41-2P 187661-42-3P 187661-43-4P
187661-44-5P 187661-45-6P 187661-46-7P
187661-47-8P 187661-48-9P 187661-49-0P
187661-50-3P 187661-51-4P 187661-52-5P
187661-53-6P 187661-54-7P 187661-55-8P
187661-56-9P 187661-57-0P 187661-59-2P
187661-60-5P 187661-61-6P 187661-62-7P
187661-63-8P 187661-64-9P 187661-65-0P
187661-66-1P 187661-67-2P 187661-68-3P
187661-69-4P 187661-70-7P 187661-71-8P
187661-72-9P 187661-73-0P 187661-74-1P
187661-75-2P 187661-76-3P 187661-77-4P
187661-78-5P 187661-79-6P 187661-80-9P
187661-81-0P 187661-82-1P 187661-83-2P
187661-85-4P 187661-87-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of tetracyclic compds. as dopamine agonists)

IT **4891-29-6P 14819-39-7P 18791-79-2P**
23074-10-4P 23229-72-3P 26963-33-7P
29212-25-7P 35491-96-4P 39251-22-4P
65601-86-7P 73540-75-7P 79757-69-0P
99186-05-7P 119030-60-3P 123418-51-9P
166591-12-4P 166591-13-5P 166591-14-6P
166591-15-7P 166591-16-8P 166591-18-0P
166591-19-1P 166591-20-4P 166591-21-5P
166591-22-6P 166591-23-7P 166591-24-8P
166591-25-9P 166591-26-0P 166591-29-3P
166591-30-6P 166591-31-7P 166591-32-8P
166591-33-9P 166591-34-0P 166591-35-1P
166591-38-4P 166591-41-9P 166591-43-1P
166591-44-2P 166591-45-3P 166591-46-4P
166591-47-5P 166591-48-6P 166591-50-0P
166591-51-1P 166591-52-2P 166591-53-3P
166591-54-4P 166591-55-5P 166591-56-6P
166591-57-7P 166591-60-2P 166591-63-5P
183874-35-3P 187660-99-7P 187661-00-3P
187661-01-4P 187661-03-6P 187661-04-7P
187661-05-8P 187661-06-9P 187661-07-0P
187661-08-1P 187661-09-2P 187661-10-5P
187661-11-6P 187661-13-8P 187661-15-0P
187661-17-2P 187661-18-3P 187661-19-4P

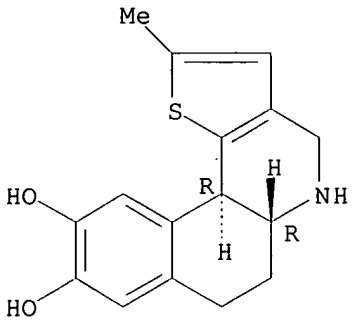
187661-20-7P 187661-21-8P 187661-22-9P
187661-25-2P 187661-28-5P 187661-31-0P
187661-33-2P 187661-34-3P 187661-35-4P
187661-36-5P 187661-37-6P 187661-38-7P
187661-39-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of tetracyclic compds. as dopamine agonists)

IT **166591-61-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of tetracyclic compds. as dopamine agonists)

IT **166590-61-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of tetracyclic compds. as dopamine agonists)

RN 166590-61-0 HCAPLUS
CN Benzo[f]thieno[3,2-c]quinoline-9,10-diol, 4,5,5a,6,7,11b-hexahydro-2-methyl-, hydrobromide, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



● HBr

L49 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2003 ACS
AN 1996:391640 HCAPLUS
DN 125:58329
TI Process for preparing chiral tetracyclic dopaminergic compounds
IN Ehrlich, Paul P.; Michaelides, Michael R.; Mclaughlin, Maureen A.; Hsaio, Chi-Nung
PA Abbott Laboratories, USA
SO PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9606085	A1	19960229	WO 1995-US9859	19950803
	W: CA, JP, MX				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 5659037	A	19970819	US 1995-463326	19950605 <--
	EP 777655	A1	19970611	EP 1995-927566	19950803
	EP 777655	B1	20010110		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	JP 10504564	T2	19980506	JP 1995-508096	19950803

AT 198592 E 20010115 AT 1995-927566 19950803
PRAI US 1994-292677 A 19940818
US 1995-463326 A 19950605
WO 1995-US9859 W 19950803
OS CASREACT 125:58329; MARPAT 125:58329
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

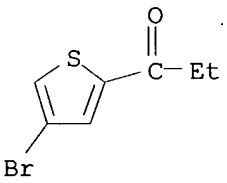
AB The title compds. [I; R = H, C1-6 alkyl; Z = O, S, CH:CH], useful as dopamine agonists (no data), were prepd. Redn. of the (R)-ketone II with NaBH4 followed by cyclization of the intermediate III (4:1 mixt. of diastereoisomers) with SnCl4, deprotection of trans-naphthylamine IV, cyclization of the intermediate V with HCHO and deprotection with BBr3 afforded (-)-I.HBr [R = Pr; Z = S].

IT **36155-78-9P 36155-79-0P 97403-64-0P**
97403-65-1P 178201-91-7P 178201-92-8P
178201-93-9P 178201-94-0P 178201-95-1P
178201-96-2P 178201-97-3P 178201-98-4P
178357-36-3P 178357-37-4P 178357-38-5P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for prepg. chiral tetracyclic dopaminergic compds.)

IT **178357-34-1P 178357-35-2P**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(process for prepg. chiral tetracyclic dopaminergic compds.)

IT **36155-78-9P**
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for prepg. chiral tetracyclic dopaminergic compds.)

RN 36155-78-9 HCAPLUS
CN 1-Propanone, 1-(4-bromo-2-thienyl)- (6CI, 9CI) (CA INDEX NAME)



References for these cmpds + parkinson -

=> d l87 bib abs hitrn fhitstr tot

L87 ANSWER 1 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 2002:555343 HCAPLUS
DN 137:103908
TI Method using D1 dopamine receptor agonists for dopamine-related dysfunction
IN **Nichols, David Earl; Mailman, Richard Bernard; Huang, Xuemei**
PA Purdue Research Foundation, USA; University of North Carolina at Chapel Hill
SO PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DT Patent

LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002056875	A2	20020725	WO 2002-US1058	20020116
	WO 2002056875	A3	20030424		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

	US 2002132827	A1	20020919	US 2002-50289	20020116
PRAI	US 2001-261889P	P	20010116		

OS MARPAT 137:103908

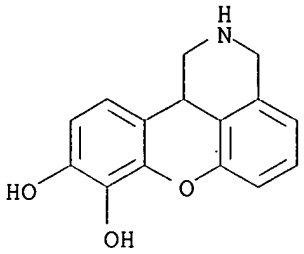
AB The invention relates to the treatment of dopamine-related dysfunction using full D1 dopamine receptor agonists in an intermittent dosing protocol with a short, but essential, "off-period". The D1 agonist concn. is reduced during the "off-period" to obtain a plasma concn. of agonist that suboptimally activates D1 dopamine receptors for a period of time to prevent induction of tolerance. Specifically, the method comprises administering to a patient a full D1 agonist with a half-life of up to about 6 h periodically at a dose resulting in a first plasma concn. of agonist capable of activating D1 dopamine receptors to produce a therapeutic effect. The dose is reduced at least once every 24 h to obtain a second lower plasma concn. of agonist which results in suboptimal activation of D1 dopamine receptors for a period of time sufficient to prevent induction of tolerance. The dopamine D1 agonist is e.g. **dinoxyline** (prepn. described). The methodol. of the invention may be used to treat e.g. **Parkinson**'s disease.

IT **313484-61-6P, Dinoxyline**
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(D1 dopamine receptor agonists for treatment of dopamine-related dysfunction)

IT **123039-93-0, Dihydrexidine 123039-93-0D, Dihydrexidine**, analogs and derivs. **221032-27-5, Dinapsoline 221032-27-5D, Dinapsoline**, analogs and derivs. **313484-61-6D, Dinoxyline**, analogs and derivs.
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(D1 dopamine receptor agonists for treatment of dopamine-related dysfunction)

IT **313484-61-6P, Dinoxyline**
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); **THU (Therapeutic use)**; **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(D1 dopamine receptor agonists for treatment of dopamine-related dysfunction)

RN 313484-61-6 HCAPLUS
CN [1]Benzopyrano[4,3,2-de]isoquinoline-8,9-diol, 1,2,3,11b-tetrahydro-, hydrobromide (9CI) (CA INDEX NAME)

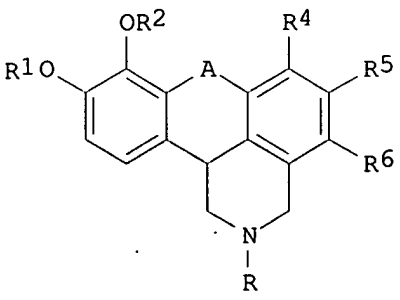


● HBr

L87 ANSWER 2 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 2002:142520 HCAPLUS
DN 136:200115
TI Preparation of **dinapsoline** and derivatives useful as dopamine receptor agonists in the treatment of movement disorders
IN Sit, Sing-Yuen; Jacutin-Porte, Swanee E.
PA Bristol-Myers Squibb Company, USA
SO PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002013827	A1	20020221	WO 2001-US25265	20010810 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2001088242	A5	20020225	AU 2001-88242	20010810 <--
	NO 2003000515	A	20030331	NO 2003-515	20030203 <--
PRAI	US 2000-224968P	P	20000811 <--		
	WO 2001-US25265	W	20010810		

OS CASREACT 136:200115; MARPAT 136:200115
GI



I

AB A process for the prepn. of compds. [I; wherein R = H, (C1-C4)alkyl; R1,

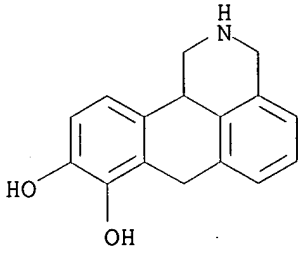
R2 = H; R4, R5, R6, independently = H, (C1-C4)alkyl, (C1-C4)alkoxy, OH, halogen; A = CH2, CHOH, C:O] is described. Thus, a multistep synthesis of N-methyl-8,9-dihydroxy-2,3,7,11b-tetrahydro-1H-naphth[1,2,3-de]isoquinoline is described. The prepd. compds. are useful for the treatment of dopamine-related disorders, particularly movement disorders (e.g., **Parkinson**'s disease).

IT **400786-40-5P**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of **dinapsoline** and derivs. useful as dopamine receptor agonists in treatment of movement disorders)

IT **400786-40-5P**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of **dinapsoline** and derivs. useful as dopamine receptor agonists in treatment of movement disorders)

RN 400786-40-5 HCAPLUS

CN 1H-Dibenz[de,h]isoquinoline-8,9-diol, 2,3,7,11b-tetrahydro-, hydrobromide (4:5) (9CI) (CA INDEX NAME)



●5/4 HBr

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

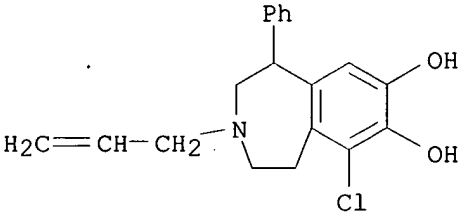
L87 ANSWER 3 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 2002:89864 HCAPLUS
DN 136:129077
TI Compounds which enhance D5-dopamine receptor activity or activation for the treatment of dyskinesia
IN Anon.
PA UK
SO PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002007766	A2	20020131	WO 2001-GB3265	20010720 <--
	WO 2002007766	A3	20020718		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,

BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRAI GB 2000-17952 A 20000722 <--
AB The invention provides compds., which enhance D5-dopamine receptor activity or activation (e.g. selective D5-dopamine receptor agonists) for use in the treatment of dyskinesia.
IT **74115-01-8**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(D5 dopamine receptor enhancers and agonists for treatment of dyskinesia)
IT **123039-93-0**
RL: PAC (Pharmacological activity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(D5 dopamine receptor enhancers and agonists for treatment of dyskinesia)
IT **74115-01-8**
RL: ADV (Adverse effect, including toxicity); **THU (Therapeutic use)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(D5 dopamine receptor enhancers and agonists for treatment of dyskinesia)
RN 74115-01-8 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)-, hydrobromide (9CI) (CA INDEX NAME)



● HBr

L87 ANSWER 4 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 2002:89830 HCAPLUS
DN 136:129075
TI Treatment of movement disorders with D5-dopamine antagonists
IN Brotchie, Jonathan
PA The Victoria University of Manchester, UK
SO PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002007726	A2	20020131	WO 2001-GB3260	20010720 <--
WO 2002007726	A3	20020906		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI GB 2000-17951 A 20000722 <--

AB The present invention relates to the use of compds. which inhibit D5-dopamine receptors, such as D5-dopamine receptor antagonists, for the treatment of movement disorders assocd. with a poverty of movement and more particularly for the treatment of **parkinsonism** (e.g. Parkinson's disease).

IT **80751-65-1**

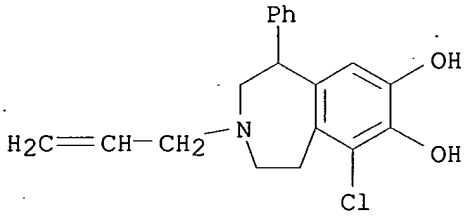
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses) (combination therapy with; treatment of movement disorders with D5-dopamine antagonists)

IT **80751-65-1**

RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses) (combination therapy with; treatment of movement disorders with D5-dopamine antagonists)

RN 80751-65-1 HCAPLUS

CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



L87 ANSWER 5 OF 66 HCAPLUS COPYRIGHT 2003 ACS

AN 2001:792337 HCAPLUS

DN 135:335185

TI Composition for the administration of a DL-agonists

IN Watts, Peter James; Illum, Lisbeth

PA West Pharmaceutical Services Drug Delivery & Clinical Research Centre Limited, UK

SO U.S., 7 pp.
CODEN: USXXAM

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 6310089	B1	20011030	US 1999-475680	19991230 <--

PRAI GB 1998-28861 A 19981231 <--

AB A compn. for intranasal administration comprising a full or partial DI-agonist of the dopamine receptor for the treatment of **Parkinson**'s disease, cognition or substance abuse is described. A D1-agonist is A-93431.1, **A 86929**.1, and ABT-431. For example, a formulation based on starch microspheres contg. A-93431.1 was prepd. A 10 mL of aq. soln. contg. 15 mg/mL of .alpha.-cyclodextrin was used to solubilize 150 mg of A-93431.1 and then 300 mg of crosslinked starch microspheres (Eldexomer) were added; the suspension of microspheres in drug soln. was adjusted to pH 4 using 0.1M HCl and then lyophilized to obtain the powder. The powder formulation was administrated at an A-93431.1 dose of 0.3 mg/kg to sheep showing improved bioavailability of A-93431.1 compared to that of i.v. injection.

IT **166591-11-3**, A 93431.1 **173934-91-3**, **A 86929**.1 **187661-43-4**

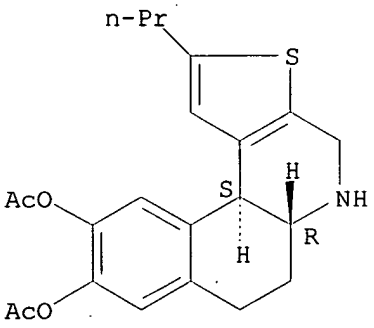
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(nasal compn. of dopamine D1-agonists for treatment of **parkinsonism**, cognition disorder and substance abuse)

IT **166591-11-3**, A 93431.1
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(nasal compn. of dopamine D1-agonists for treatment of **parkinsonism**, cognition disorder and substance abuse)

RN 166591-11-3 HCAPLUS

CN Benzo[f]thieno[2,3-c]quinoline-9,10-diol, 4,5,5a,6,7,11b-hexahydro-2-propyl-, diacetate (ester), hydrochloride, (5aR,11bS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 6 OF 66 HCAPLUS COPYRIGHT 2003 ACS

AN 2001:730538 HCAPLUS

DN 135:267255

TI Metabotropic glutamate receptor inhibitors, and use with other agents, for the treatment of movement disorders

IN Brotchie, Jonathan; Hill, Michael; Crossman, Alan

PA The Victoria University of Manchester, UK

SO PCT Int. Appl., 24 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001072291	A2	20011004	WO 2001-GB1279	20010323 <--
WO 2001072291	A3	20020221		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,

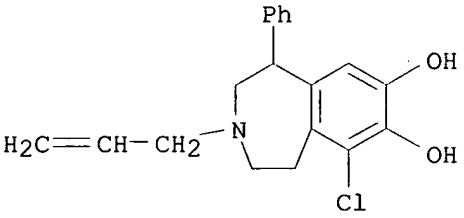
BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
EP 1274417 A2 20030115 EP 2001-915476 20010323 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
US 2003109504 A1 20030612 US 2002-239710 20021114 <--
PRAI GB 2000-7193 A 20000325 <--
WO 2001-GB1279 W 20010323

AB The invention disclose the use of compds. which inhibit metabotropic glutamate receptor activity or activation for use in the treatment of movement disorders assocd. with a poverty of movement (e.g. **Parkinson**'s disease). The compds. are particularly useful when used in combination with another therapeutic agent and surprisingly reduce the extent and incidence of side effects (e.g. dyskinesia) assocd. with such therapeutic agents.

IT **80751-65-1**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(metabotropic glutamate receptor inhibitors, and use with other agents, for treatment of movement disorders)

IT **80751-65-1**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(metabotropic glutamate receptor inhibitors, and use with other agents, for treatment of movement disorders)

RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



L87 ANSWER 7 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 2001:319723 HCAPLUS
DN 134:320875
TI H3-histamine receptor modulator for treatment of dyskinesia
IN Brotchie, Jonathan; Hill, Michael; Crossman, Alan
PA The Victoria University of Manchester, UK
SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001030346	A1	20010503	WO 2000-GB4046	20001020 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,

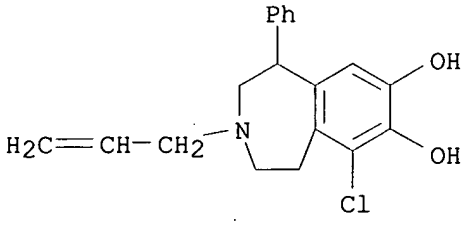
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
EP 1223930 A1 20020724 EP 2000-972966 20001020 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL
JP 2003512428 T2 20030402 JP 2001-532766 20001020 <--
PRAI GB 1999-24941 A 19991022 <--
WO 2000-GB4046 W 20001020 <--

AB The invention discloses the use of compds. that enhance H3-histamine receptor activity or activation (e.g. H3-histamine receptor agonists) for the treatment of dyskinesia. The compds. are particularly useful for treating dyskinesia assocd. with **parkinsonian** therapy.

IT **80751-65-1**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(H3-histamine receptor modulator for treatment of dyskinesia)

IT **80751-65-1**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(H3-histamine receptor modulator for treatment of dyskinesia)

RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

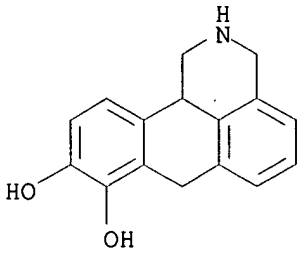
L87 ANSWER 8 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 2001:126013 HCAPLUS
DN 134:340412
TI An efficient synthesis of the potent dopamine D1 agonist **dinapsoline** by construction and selective reduction of 2'-azadimethoxybenzanthrone
AU Sattelkau, Tim; Qandil, Amjad M.; **Nichols, David E.**
CS Department of Medicinal Chemistry and Molecular Pharmacology, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN, 47907, USA
SO Synthesis (2001), (2), 262-266
CODEN: SYNTBF; ISSN: 0039-7881
PB Georg Thieme Verlag
DT Journal
LA English
OS CASREACT 134:340412
AB 8,9-Dihydroxy-2,3,7,11b-tetrahydro-1H-naphth[1,2,3-de]isoquinoline (**dinapsoline**) is a potent dopamine D1 receptor agonist with potential **antiparkinsonian** activity. A new synthesis was developed with the fully arom. 8,9-dimethoxy-7H-dibenz[de,h]isoquinolin-7-one as the key intermediate. The synthesis herein described is suitable for a larger scale prepn. of **dinapsoline** compared to the previously known methods. Furthermore, the unproductive

protection/deprotection step of the nitrogen is circumvented by maintaining a high oxidn. state of the isoquinoline moiety throughout the synthesis. The construction of the framework was accomplished by Friedel-Crafts acylation and a Suzuki cross-coupling reaction between the com. available 4-bromoisoquinoline and aryl boronic acid intermediate, the latter demanding the transformation of the lithiation-directing amide back to a carboxylic acid functionality. The selective redn. was carried out stepwise with sodium borohydride and sodium cyanoborohydride. The new synthesis is high yielding and reduces the no. of transformations in the previously reported methods.

IT **221032-27-5P, Dinapsoline**
RL: PNU (Preparation, unclassified); PREP (Preparation)
(prepn. of dopamine D1 agonist **dinapsoline** by construction and selective redn. of dimethoxy-7H-dibenz[de,h]isoquinolinone)

IT **221032-27-5P, Dinapsoline**
RL: PNU (Preparation, unclassified); PREP (Preparation)
(prepn. of dopamine D1 agonist **dinapsoline** by construction and selective redn. of dimethoxy-7H-dibenz[de,h]isoquinolinone)

RN 221032-27-5 HCAPLUS
CN 1H-Dibenz[de,h]isoquinoline-8,9-diol, 2,3,7,11b-tetrahydro- (9CI) (CA INDEX NAME)



RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

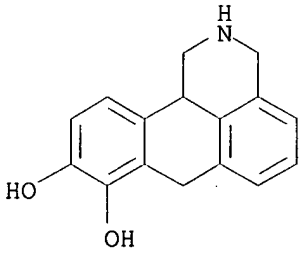
L87 ANSWER 9 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 2001:87281 HCAPLUS
DN 134:125884
TI **Dinapsoline**: characterization of a D1 dopamine receptor agonist in a rat model of **Parkinson**'s disease
AU Gulwadi, Amit G.; Korpinen, Carolyn D.; **Mailman, Richard B.**; **Nichols, David E.**; Sit, Sing-Yuen; Taber, Matthew T.
CS Neuroscience/Genitourinary Drug Discovery, Bristol-Myers Squibb Inc., Wallingford, CT, USA
SO Journal of Pharmacology and Experimental Therapeutics (2001), 296(2), 338-344
CODEN: JPETAB; ISSN: 0022-3565
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
AB **Dinapsoline** is a new potent, full agonist at D1 dopamine receptors with limited selectivity relative to D2 receptors. The efficacy of this compd. was assessed in rats with unilateral 6-hydroxydopamine lesions of the medial forebrain bundle, a std. rat model of **Parkinson**'s disease. **Dinapsoline** produced robust contralateral rotation after either s.c. or oral administration. This rotational behavior was attenuated markedly by the D1 receptor antagonist SCH-23390, but not by the D2 receptor antagonist raclopride. During a chronic 14-day treatment period in which rats received **dinapsoline** either once or twice a day, **dinapsoline** did not produce tolerance (in fact, some sensitization of the rotational response was

obsd. in one expt.). Because **dinapsoline** shows less D1:D2 selectivity in vitro than other D1 agonists, the contribution of D2 activity to tolerance was assessed. Chronic daily cotreatment with **dinapsoline** and raclopride did not enable the development of tolerance to chronic **dinapsoline** treatment. In contrast, when **dinapsoline** was administered by osmotic minipump, rapid tolerance was obsd. To explore further the contribution of D1 and D2 receptors to tolerance, expts. were performed with the selective D1 agonist A-77636. Daily dosing with A-77636 rapidly produced complete tolerance, as previously obsd., whereas coadministration of the D2 agonist quinpirole plus A-77636 failed to either delay or prevent tolerance. Taken together, these results indicate that the development of tolerance to D1 receptor agonists is influenced by the pattern of drug exposure but not by the D1:D2 selectivity of the agonist.

IT **221032-27-5, Dinapsoline**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(**dinapsoline** effect on rotational behavior and tolerance in **Parkinson**'s disease model mediation by dopaminergic receptor subtypes)

IT **221032-27-5, Dinapsoline**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(**dinapsoline** effect on rotational behavior and tolerance in **Parkinson**'s disease model mediation by dopaminergic receptor subtypes)

RN 221032-27-5 HCAPLUS
CN 1H-Dibenz[de,h]isoquinoline-8,9-diol, 2,3,7,11b-tetrahydro- (9CI) (CA INDEX NAME)



RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

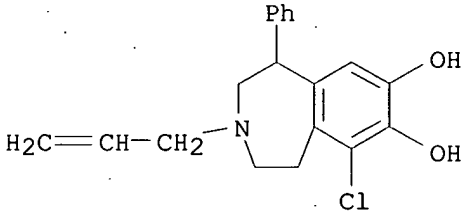
L87 ANSWER 10 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 2001:51648 HCAPLUS
DN 134:188451
TI Dopaminergic regulation of synaptotagmin I and IV mRNAs in **hemiparkinsonian** rats
AU Glavan, Gordana; Zorec, Robert; Babic, Ksenja; Sket, Dusan; Zivin, Marko
CS Brain Res. Lab., Univ. Ljubljana, Ljubljana, 1000, Slovenia
SO NeuroReport (**2000**), 11(18), 4043-4047
CODEN: NERPEZ; ISSN: 0959-4965
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Synaptotagmin (syt) I and IV are synaptic proteins involved in the regulation of neurosecretion. Dopaminergic drugs have been shown to modulate their expression. Here we investigate whether dopaminergic regulation of syt I and syt IV expression could play a role in the

hypersensitive striatum of rats with unilateral lesions of dopaminergic nigrostriatal neurons with 6-hydroxydopamine. We slow that chronic dopaminergic denervation resulted in a small down-regulation of striatal syt I mRNA, whereas acute treatment with **SKF-82958**, a dopamine D1 receptor agonist, induced a massive syt IV mRNA up-regulation in the striatum on the lesioned side. We conclude that chronic lack of dopamine and treatment with dopamine D1 receptor agonists alter the synaptic plasticity in dopamine depleted basal ganglia.

IT **80751-65-1, SKF-82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(dopaminergic regulation of striatal synaptotagmin I and IV mRNA expression in **hemiparkinsonian** rats)

IT **80751-65-1, SKF-82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(dopaminergic regulation of striatal synaptotagmin I and IV mRNA expression in **hemiparkinsonian** rats)

RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

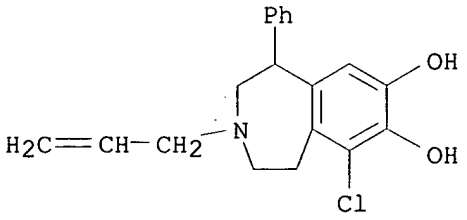
L87 ANSWER 11 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 2000:678023 HCAPLUS
DN 134:36940
TI Enhancement of the acoustic startle response by dopamine agonists after 6-hydroxydopamine lesions of the substantia nigra pars compacta: corresponding changes in c-Fos expression in the caudate-putamen
AU Meloni, E. G.; Davis, M.
CS Department of Psychiatry and Behavioral Sciences, Emory University, Atlanta, GA, 30322, USA
SO Brain Research (**2000**), 879(1,2), 93-104
CODEN: BRREAP; ISSN: 0006-8993
PB Elsevier Science B.V.
DT Journal
LA English
AB Rats with 6-hydroxydopamine (6-OHDA) lesions of the nigrostriatal pathway show enhanced locomotor and stereotyped behaviors when challenged with direct and indirect dopamine (DA) agonists due to the development of postsynaptic supersensitivity. To det. if this phenomenon generalizes to other motor behaviors, we have used this rat model of **Parkinson**'s disease to examine the effects of the direct dopamine D1 receptor agonist **SKF 82958** and the indirect DA agonist l-3,4-dihydroxyphenylalanine (l-DOPA) on the acoustic startle response. In addn., we used the expression of c-Fos protein as a marker of neuronal activity to assess any corresponding drug-induced changes in the caudate-putamen (CPu) after l-DOPA administration. Male Sprague-Dawley rats received bilateral injections of 6-OHDA into the substantia nigra pars compacta and 1 wk later were tested for startle after systemic

administration of **SKF 82958** (0.05 mg/kg) or l-DOPA (1, 5, 10 mg/kg). **SKF 82958** produced a marked enhancement of startle with a rapid onset in 6-OHDA-lesioned but not SHAM animals. l-DOPA produced a dose- and time-dependent enhancement of startle in 6-OHDA-lesioned rats that had no effect in SHAM animals even at the highest dose (10 mg/kg). Furthermore, l-DOPA produced a dramatic induction of c-Fos in the CPu in 6-OHDA-lesioned animals. Consistent with other literature, these data suggest that neurons in the CPu become supersensitive to the effects of DA agonists after 6-OHDA-induced denervation of the nigrostriatal pathway and that supersensitive dopamine D1 receptors may mediate the enhancement of startle seen in the present study.

IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(enhancement of acoustic startle response by dopamine agonists after 6-OHDAlesions of substantia nigra pars compacta: changes in c-Fos expression in caudate-putamen)

IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(enhancement of acoustic startle response by dopamine agonists after 6-OHDAlesions of substantia nigra pars compacta: changes in c-Fos expression in caudate-putamen)

RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



RE.CNT 79 THERE ARE 79 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

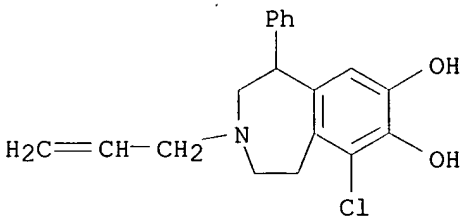
L87 ANSWER 12 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 2000:587870 HCAPLUS
DN 133:305508
TI Dopamine D1 agonist activates temporal lobe structures in primates
AU Black, Kevin J.; Hershey, Tamara; Gado, Mokhtar H.; Perlmutter, Joel S.
CS Departments of Psychiatry, Neurology and Neurological Surgery, Radiology, The Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO, 63110, USA
SO Journal of Neurophysiology (**2000**), 84(1), 549-557
CODEN: JONEA4; ISSN: 0022-3077
PB American Physiological Society
DT Journal
LA English
AB Changes in the function of dopamine D1-influenced neuronal pathways may be important to the pathophysiol. of several human diseases. We recently developed methods for averaging functional imaging data across nonhuman primate subjects; in this study, we apply this method for the first time to map brain responses to exptl. dopamine agonists in vivo. Here we report the use of positron emission tomog. (PET) in seven normal baboons

to measure the regional cerebral blood flow (rCBF) responses produced by an acute dose of the dopamine D1 full agonist **SKF82958**. The most significant rCBF increases were in bilateral temporal lobe, including amygdala and superior temporal sulcus (6-17%, P < 0.001). Blood flow decreased in thalamus, pallidum, and pons (4-7%, P = 0.001). Furthermore the rCBF responses were dose-dependent and had a half-life of .apprx.30 min, similar to that reported for the drug's **antiparkinsonian** effects. Abs. whole-brain blood flow did not change, suggesting that these local changes in rCBF reflect neuronal rather than direct vascular effects of the agonist. The prominent temporal lobe response to a D1 agonist supports and extends our recent observations that levodopa produces prominent amygdala activation both in humans and in other primates. We speculate that levodopa may exert its known effects on mood in humans through increased amygdala activity, mediated in part by D1 receptors.

IT **80751-65-1, SKF82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(dopamine D1 agonist activates temporal lobe structures in primates)

IT **80751-65-1, SKF82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(dopamine D1 agonist activates temporal lobe structures in primates)

RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



RE.CNT 114 THERE ARE 114 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

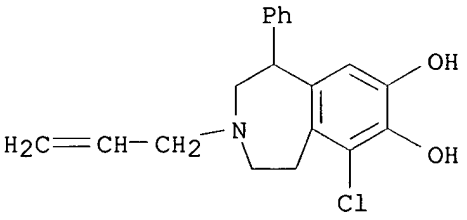
L87 ANSWER 13 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 2000:400587 HCAPLUS
DN 133:129790
TI 5-HT2C receptor antagonists enhance the behavioural response to dopamine D1 receptor agonists in the 6-hydroxydopamine-lesioned rat
AU Fox, S. H.; Brotchie, J. M.
CS Manchester Movement Disorder Laboratory, Division of Neuroscience, School of Biological Sciences, University of Manchester, Manchester, M13 9PT, UK
SO European Journal of Pharmacology (**2000**), 398(1), 59-64
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier Science B.V.
DT Journal
LA English
AB Non-dopaminergic therapies are of potential interest in the treatment of **Parkinson**'s disease given the complications assocd. with current dopamine-replacement therapies. In this study we demonstrate that SB 206553 (5-methyl-1-(3-pyridylcarbamoyl)-1,2,3,5-tetrahydropyrrol[2,3-f]indole) (20 mg/kg) enhanced the actions of the dopamine D1 receptor agonist, **SKF 82958** ((+)-6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide) (1 mg/kg), in eliciting locomotion in the 6-hydroxydopamine-lesioned rat model of **Parkinson**'s disease. This action was only seen following prior

priming with L-DOPA (L-3,4-dihydroxyphenylalanine). SB 206553 had no effect on rotational behavior when given alone. 5-HT2C receptor antagonists may have potential as a means of reducing reliance on dopamine replacement in the treatment of **Parkinson**'s disease.

IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(5-HT2C receptor antagonists enhance behavioral response to dopamine D1 receptor agonists in rat model of **Parkinson**'s disease)

IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(5-HT2C receptor antagonists enhance behavioral response to dopamine D1 receptor agonists in rat model of **Parkinson**'s disease)

RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

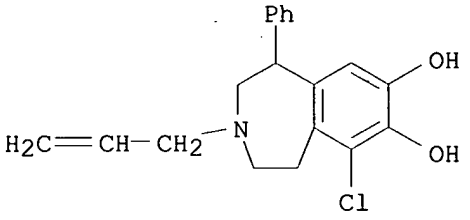
L87 ANSWER 14 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 2000:274433 HCAPLUS
DN 133:280016
TI 125I-CGP 64213 binding to GABAB receptors in the brain of monkeys: effect of MPTP and dopaminomimetic treatments
AU Calon, Frederic; Morissette, Marc; Goulet, Martin; Grondin, Richard; Blanchet, Pierre J.; Bedard, Paul J.; Di Paolo, Therese
CS Oncology and Molecular Endocrinology Research Center, Laval University Medical Center (CHUL), Quebec, QC, G1V 4G2, Can.
SO Experimental Neurology (**2000**), 163(1), 191-199
CODEN: EXNEAC; ISSN: 0014-4886
PB Academic Press
DT Journal
LA English
AB Much evidence indicates that abnormal GABA neurotransmission may be implicated in the pathophysiol. of **Parkinson**'s disease (PD) and dopaminomimetic-induced dyskinesias (DID). In this study, autoradiog. using 125I-CGP 64213 was performed to investigate GABAB receptor d. in the brain of control monkeys as well as monkeys with MPTP-induced nigrostriatal depletion. Three MPTP monkeys received pulsatile administrations of the D1 dopamine (DA) receptor agonist (**SKF 82958**), whereas a long-acting D2 DA receptor agonist (cabergoline) was given to another three animals. **SKF 82958** treatment relieved **parkinsonian** symptoms but two of three animals developed DID. Cabergoline induced a comparable motor benefit effect without persistent DID. 125I-CGP 64213 binding to GABAB receptors was heterogeneous throughout the brain with the highest levels in the medial habenula of the thalamus. MPTP induced a decrease (-40%) of 125I-CGP 64213 binding to GABAB receptors in the substantia nigra pars compacta (SNpc) and an increase (+29%) in the internal segment of the globus pallidus (GPi). This increase in the GPi was not affected by

SKF 82958 but partly reversed by cabergoline. No change was seen in the striatum, the thalamus, the external segment of the globus pallidus, and the substantia nigra pars reticulata following MPTP and dopaminomimetic treatments. The changes of GABAB receptors obsd. in the SNpc and in the GPi suggest that alteration of GABAB receptors may play a role in the pathophysiol. of PD and DID. (c) 2000 Academic Press.

IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(125I-CGP 64213 binding to GABAB receptors in brain of monkeys: effect of MPTP and dopaminomimetic treatments)

IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(125I-CGP 64213 binding to GABAB receptors in brain of monkeys: effect of MPTP and dopaminomimetic treatments)

RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



RE.CNT 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 15 OF 66. HCAPLUS COPYRIGHT 2003 ACS
AN 2000:248644 HCAPLUS
DN 133:12675
TI The effects of central aromatic amino acid DOPA decarboxylase inhibition on the motor actions of L-DOPA and dopamine agonists in MPTP-treated primates
AU Treseder, Sarah A.; Jackson, Michael; Jenner, Peter
CS Neurodegenerative Disease Research Centre, Division of Pharmacology & Therapeutics, Guy's, King's and St Thomas' School of Biomedical Sciences, King's College, London, SE1 1UL, UK
SO British Journal of Pharmacology (**2000**), 129(7), 1355-1364
CODEN: BJPCBM; ISSN: 0007-1188
PB Nature Publishing Group
DT Journal
LA English
AB Endogenous L-DOPA may act as a neuromodulator contributing to the prodn. of motor activity. We now investigate the effects of the centrally acting arom. amino acid dopa decarboxylase (AADC) inhibitor NSD-1015 (3-hydroxybenzyl hydrazine) on the motor actions of L-DOPA and dopamine agonist drugs in MPTP treated common marmosets. Pretreatment with NSD-1015 (10-50 mg kg-1; i.p.) worsened baseline motor deficits in MPTP-treated common marmosets. Similarly, it abolished L-DOPA (5-18 mg kg-1 s.c.) induced locomotor activity and reversal of disability. NSD-1015 pretreatment inhibited dopamine formation and elevated L-DOPA levels in plasma. The increase in locomotor activity and improvement in disability produced by the administration of the D-1 agonist **A-86929** (0.03-0.04 mg kg-1 s.c.) or the D-2 agonist quinpirole

(0.05-0.3 mg kg-1 i.p.) was abolished by NSD-1015 (25 mg kg-1 i.p.) pretreatment. While the effects of a low dose combination of **A-86929** (0.04 mg kg-1 s.c.) and quinpirole (0.05 mg kg-1 i.p.) were inhibited by NSD-1015 (25 mg kg-1 i.p.), there was little effect on the action of a high dose combination of these drugs (0.08 mg kg-1 **A-86929** and 0.1 mg kg-1 quinpirole). Following central AADC inhibition with NSD-1015 (25 mg kg-1 i.p.), locomotor behavior induced by administration of high dose combinations of **A-86929** (0.08 mg kg-1 s.c.) and quinpirole (0.1 mg kg-1 i.p.) was unaffected by L-DOPA (5 mg kg-1 s.c.) pretreatment. These results do not support a role for endogenous L-DOPA in spontaneous or drug induced locomotor activity. Rather, they strengthen the argument for the importance of endogenous dopaminergic tone in the motor actions of dopamine agonists.

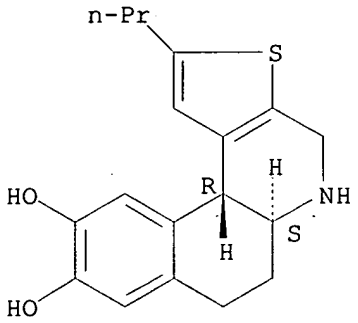
IT **173934-91-3, A-86929**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(role of L-DOPA in motor actions of dopamine agonists in MPTP-treated primates)

IT **173934-91-3, A-86929**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(role of L-DOPA in motor actions of dopamine agonists in MPTP-treated primates)

RN 173934-91-3 HCAPLUS

CN Benzo[f]thieno[2,3-c]quinoline-9,10-diol, 4,5,5a,6,7,11b-hexahydro-2-propyl-, hydrochloride, (5aR,11bS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



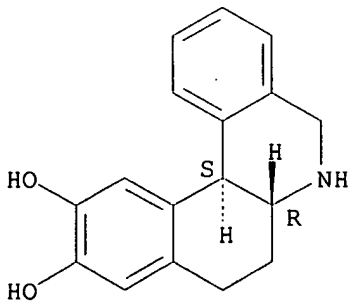
● HCl

RE.CNT 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 16 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 2000:81361 HCAPLUS
DN 132:216994
TI D1 dopamine receptor agonists are more effective in alleviating advanced than mild **parkinsonism** in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated monkeys
AU Goulet, Martin; Madras, Bertha K.
CS New England Regional Primate Research Center, Division of Neurochemistry, Harvard Medical School, Southborough, MA, USA
SO Journal of Pharmacology and Experimental Therapeutics (**2000**), 292(2), 714-724
CODEN: JPETAB; ISSN: 0022-3565
PB American Society for Pharmacology and Experimental Therapeutics

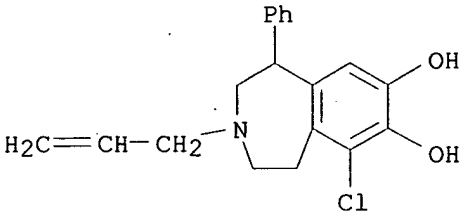
DT Journal
LA English
AB Selective D1 dopamine receptor agonists exert **antiparkinsonian** effects in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkey model of **Parkinson**'s disease and in human **Parkinson**'s disease. Motor impairment in idiopathic **Parkinson**'s disease progresses from mild to severe, but the therapeutic potential of D1 dopamine receptor agonists in early and advanced stages of **parkinsonism** is not known. To compare the effectiveness of D1 agonists at different levels of impairment, we developed a model of mild and advanced **parkinsonism** in nonhuman primates and a rating scale that differentiated the two models. D1 dopamine receptor agonists (SKF 81297, **dihydrexidine**) and D2 dopamine receptor agonists [quinelorane, (+)-PHNO] were administered to monkeys (Macaca fascicularis) displaying either mild **parkinsonism** (two doses of 0.6 mg/kg i.v. MPTP 1 mo apart) or advanced **parkinsonism** (three doses of 0.6 mg/kg i.v. MPTP within 10 days). In normal monkeys (n = 3), SKF 81297 and **dihydrexidine** did not promote increased motor activity. In advanced **parkinsonism** (n = 4), D1 and D2 dopamine agonists effectively reversed the motor deficits. In contrast, the therapeutic benefits of D1 agonists SKF 81297 and **dihydrexidine** were relatively limited in mild **parkinsonism** (n = 4). The D2 agonists quinelorane and (+)-PHNO alleviated some symptoms in mild **parkinsonism** but also reduced balance and induced more dyskinesias than did D1 agonists. Mild and advanced **parkinsonism** in nonhuman primates can be produced with fixed dosing regimens of MPTP. Based on the therapeutic efficacy and side effect profiles derived from these models, D1 agonists are more promising for the treatment of advanced than of mild **Parkinson**'s disease.
IT **123039-93-0, Dihydrexidine**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(effect of D1 dopamine receptor agonists in alleviating advanced than mild vs. advanced **parkinsonism** in MPTP-treated monkey model)
IT **123039-93-0, Dihydrexidine**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(effect of D1 dopamine receptor agonists in alleviating advanced than mild vs. advanced **parkinsonism** in MPTP-treated monkey model)
RN 123039-93-0 HCAPLUS
CN Benzo[a]phenanthridine-10,11-diol, 5,6,6a,7,8,12b-hexahydro-, (6aR,12bS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RE.CNT 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 17 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1999:606176 HCAPLUS
DN 131:295498
TI Dopamine D1 receptor mRNA and receptor levels in the striatum of MPTP monkeys chronically treated with **SKF-82958**
AU Grondin, Richard; Goulet, Martin; Morissette, Marc; Bedard, Paul J.; Di Paolo, Therese
CS Faculty of Medicine, Laval University, Quebec City, QC, G1K 7P4, Can.
SO European Journal of Pharmacology (**1999**), 378(3), 259-263
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier Science B.V.
DT Journal
LA English
AB The d. of dopamine D1 receptor antagonist sites was measured by autoradiog. and dopamine D1 receptor mRNA levels were measured by in situ hybridization in the striatum of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-exposed monkeys chronically treated with the dopamine D1 receptor agonist 6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide (**SKF-82958**) administered in intermittent or continuous mode for a month. Normal and MPTP-exposed but otherwise untreated animals were used for comparison. Intermittent treatment with **SKF-82958** relieved **parkinsonian** features and induced dyskinesias whereas given continuously this drug induced behavioral tolerance without dyskinesias. On the one hand, MPTP treatment tended to increase dopamine D1 receptor d. in the putamen whereas treatment of MPTP monkeys with **SKF-82958**, intermittent or continuous, produced a significant increase compared to control animals. Dopamine D1 receptor mRNA levels in the putamen appeared to decrease after MPTP lesion and agonist treatment as compared to dopamine D1 receptor d. In contrast, an apparent decrease in dopamine D1 receptor d. and mRNA levels was obsd. in the nucleus accumbens of untreated MPTP monkeys whereas treatment of MPTP monkeys with **SKF-82958**, intermittent or continuous, produced a significant decrease compared to control animals. Thus, neither dyskinesias nor tolerance can be exclusively related to an increase or decrease in striatal dopamine D1 receptors, resp.
IT **80751-65-1, SKF-82958**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(dopamine D1 receptor mRNA and receptor levels in striatum of MPTP monkeys chronically treated with dopamine agonist **SKF-82958** in relation to **parkinsonism** treatment and dyskinesia and tolerance)
IT **80751-65-1, SKF-82958**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(dopamine D1 receptor mRNA and receptor levels in striatum of MPTP monkeys chronically treated with dopamine agonist **SKF-82958** in relation to **parkinsonism** treatment and dyskinesia and tolerance)
RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

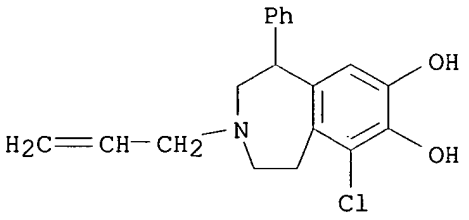
L87 ANSWER 18 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1999:434082 HCAPLUS
DN 131:266877
TI The predictive validity of the drug-naive bilaterally MPTP-treated monkey as a model of **Parkinson**'s disease: effects of L-DOPA and the D1 agonist **SKF 82958**
AU Andringa, G.; Lubbers, L.; Drukarch, B.; Stoof, J. C.; Cools, A. R.
CS Research Institute of Neuroscience, Department of Neurology, Vrije Universiteit of Amsterdam, Amsterdam, Neth.
SO Behavioural Pharmacology (**1999**), 10(2), 175-182
CODEN: BPHAEL; ISSN: 0955-8810
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB The aim of this study was 2-fold: (1) to study the predictive validity of the drug-naive, bilaterally MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-HCl)-treated monkey as an animal model of **Parkinson**'s disease (PD), and (2) to investigate the therapeutic and undesired effects of the D1 agonist **SKF 82958** as compared to L-DOPA treatment, in drug-naive and L-DOPA pretreated monkeys. A detailed ethogram was used, allowing the sepn. of therapeutic and undesired effects. Eight weeks after bilateral intracarotid MPTP administration, **SKF 82958** (1 mg/kg, **SKF 82958**-naive group) or methyl-L-DOPA plus carbidopa (10 plus 2.5 mg/kg, L-DOPA group) was administered i.m. for 22 days. After a drug-free period of 8 wk, the L-DOPA group was treated with **SKF 82958** for 22 days (SKF 82959, 1 mg/kg, pretreated). All the drug treatments increased the parameters used classically to evaluate dopaminergic drugs, namely, body displacement, dyskinesia and dystonia. However, the new detailed anal. revealed that L-DOPA, but not **SKF 82958**, had therapeutic effects, reflected by an increase in goal-directed forelimb use. **SKF 82958**, but not L-DOPA, induced addnl. undesired effects, including epileptoid behaviors, in both drug-naive and drug-pretreated monkeys. In one L-DOPA-unresponsive monkey, **SKF 82958** did induce minor therapeutic effects, as well as undesired effects. Although the effects of **SKF 82958** on forelimb movements, rotational behaviors and body displacement were comparable in the naive and pretreated groups, **SKF 82958** reinitiated undesired effects in the L-DOPA-pretreated group from day one. It is concluded that the bilaterally MPTP-treated monkey is an animal model with predictive validity for PD: it adequately predicts the therapeutic effects and undesired effects of L-DOPA. Furthermore, it is concluded that **SKF 82958** is less effective than L-DOPA in the treatment of PD, because it did not induce therapeutic effects, but instead elicited several undesired effects.
IT **80751-65-1, SKF 82958**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU**

(Therapeutic use); BIOL (Biological study); USES (Uses)
(dopa and **SKF 82958** effects in the drug-naive bilaterally MPTP-treated monkey as a model of **Parkinson**'s disease)

IT **80751-65-1, SKF 82958**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(dopa and **SKF 82958** effects in the drug-naive bilaterally MPTP-treated monkey as a model of **Parkinson**'s disease)

RN 80751-65-1 HCAPLUS

CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 19 OF 66 HCAPLUS COPYRIGHT 2003 ACS

AN 1999:412107 HCAPLUS

DN 131:179747

TI Chronic D1 and D2 dopaminomimetic treatment of MPTP-denervated monkeys: effects on basal ganglia GABAA/benzodiazepine receptor complex and GABA content

AU Calon, Frederic; Morissette, Marc; Goulet, Martin; Grondin, Richard; Blanchet, Pierre J.; Bedard, Paul J.; Di Paolo, Therese

CS Centre de Recherches en Endocrinologie Moleculaire, Le Centre Hospitalier Universitaire de Quebec, Pavillon CHUL, QC, G1V 4G2, Can.

SO Neurochemistry International (**1999**), 35(1), 81-91
CODEN: NEUIDS; ISSN: 0197-0186

PB Elsevier Science Ltd.

DT Journal

LA English

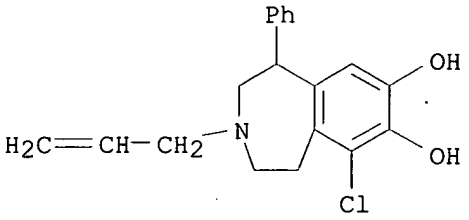
AB The effect of various chronic dopaminergic treatments in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkeys on the brain .gamma.-aminobutyric acid type A (GABAA)/benzodiazepine receptor complex and GABA content was investigated to assess the GABAergic involvement in dopaminomimetic-induced dyskinesia. Three MPTP monkeys received for one month pulsatile administrations of the D1 dopamine (DA) receptor agonist **SKF 82958**, whereas three others received the same dose of **SKF 82958** by continuous infusion. A long acting D2 DA receptor agonist, cabergoline, was given to another three animals. Untreated MPTP as well as naive control animals were also included. Pulsatile **SKF 82958** relieved **parkinsonian** symptoms but was also assocd. with dyskinesia in two of the three animals, whereas animals treated continuously with **SKF 82958** remained as untreated MPTP monkeys. Chronic cabergoline administration improved motor response with no persistent dyskinesia. MPTP treatment induced a decrease of 3H-flunitrazepam binding in the medial anterior part of caudate-putamen and an increase in the internal segment of globus pallidus (GPi) which was in general unchanged by pulsatile or continuous **SKF 82958** administration. Throughout the striatum,

binding of 3H-flunitrazepam remained reduced in MPTP monkeys treated with cabergoline but was not significantly lower than untreated MPTP monkeys. Moreover, cabergoline treatment reversed the MPTP-induced increase in 3H-flunitrazepam binding in the GPi. GABA concns. remained unchanged in the striatum, external segment of globus pallidus and GPi following MPTP denervation. Pulsatile but not continuous **SKF 82958** administration decreased putamen GABA content, whereas cabergoline treatment decreased caudate GABA. No alteration in GABA levels were obsd. in the GPe and GPi following the exptl. treatments. These results suggest that: (1) D2-like receptor stimulation with cabergoline modulates GABAA receptor d. in striatal subregions anatomically related to associative cortical afferent and (2) the absence of dyskinesia in dopaminomimetic-treated monkeys might be assocd. with the reversal of the MPTP-induced upregulation of the GABAA/benzodiazepine receptor complex in the Gpi.

IT **80751-65-1, SKF 82958**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(D1 and D2 dopaminomimetic effects on basal ganglia GABAA/benzodiazepine receptor complex and GABA content in MPTP-denervated monkey model of **Parkinsonism**)

IT **80751-65-1, SKF 82958**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(D1 and D2 dopaminomimetic effects on basal ganglia GABAA/benzodiazepine receptor complex and GABA content in MPTP-denervated monkey model of **Parkinsonism**)

RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



RE.CNT 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 20 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1999:402723 HCAPLUS
DN 131:82910
TI ABT-431, a D1 receptor agonist prodrug, has efficacy in **Parkinson**'s disease
AU Rascol, O.; Blin, O.; Thalamas, C.; Descombes, S.; Soubrouillard, C.; Azulay, P.; Fabre, N.; Viallet, F.; Lafnitzegger, K.; Wright, S.; Carter, J. H.; Nutt, J. G.
CS Clinical Investigation Centre, Departments of Pharmacology and Neurology, INSERM U455, University Hospital, Toulouse, Fr.
SO Annals of Neurology (**1999**), 45(6), 736-741
CODEN: ANNED3; ISSN: 0364-5134
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Studies in animal models show a selective D1 receptor agonist with full

functional efficacy compared with dopamine to have **antiparkinsonian** efficacy of similar magnitude to levodopa, without the same propensity for inducing dyskinesia. To date, no such agent has been tested in humans. ABT-431 is the prodrug of **A-86929**, a full, selective D1 receptor agonist. Subjects (n = 14) with levodopa-responsive **Parkinson**'s disease received five doses of ABT-431 (5, 10, 20, 30, and 40 mg) and one of placebo after a 12-h levodopa holiday. Response was assessed by using the Unified **Parkinson**'s Disease Rating Scale motor subsection. Dyskinesia was sep. graded. ABT-431 showed efficacy significantly superior to placebo at doses of 10 mg and more, and of similar magnitude to that seen with levodopa. Dyskinesia was reduced in several patients after receiving ABT-431. There were no serious adverse events, the most common minor events being nausea and emesis, dizziness, and hypotension. Assuming that ABT-431 is not transformed in humans into an unknown active D2 metabolite, and remains selective for D1 receptors, it is the first dopamine D1 receptor agonist to demonstrate a full **antiparkinsonian** effect in patients with **Parkinson**'s disease. These preliminary findings also suggest that it may exhibit a reduced tendency to provoke dyskinesia. The emergence of a well-tolerated D1 agonist should allow for the development of a better understanding of the relation between motor efficacy and dyskinesia in **Parkinson**'s disease.

IT **166591-11-3**, ABT-431
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ABT-431, a D1 receptor agonist treatment for **Parkinson**'s disease in humans)

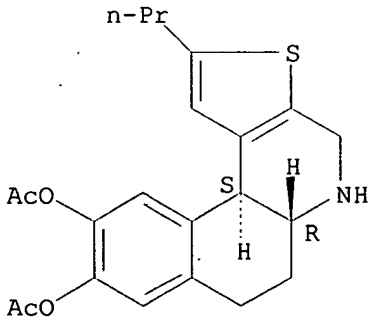
IT **173934-91-3, A-86929**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ABT-431, a D1 receptor agonist treatment for **Parkinson**'s disease in humans)

IT **166591-11-3**, ABT-431
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ABT-431, a D1 receptor agonist treatment for **Parkinson**'s disease in humans)

RN 166591-11-3 HCAPLUS

CN Benzo[f]thieno[2,3-c]quinoline-9,10-diol, 4,5,5a,6,7,11b-hexahydro-2-propyl-, diacetate (ester), hydrochloride, (5aR,11bS)- (9CI) (CA INDEX NAME)

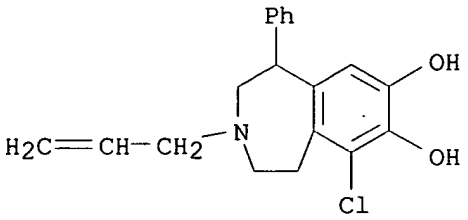
Absolute stereochemistry.



HCl

RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 21 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1999:386006 HCAPLUS
DN 131:139840
TI Effects of intrasubthalamic injection of dopamine receptor agonists on subthalamic neurons in normal and 6-hydroxydopamine-lesioned rats: an electrophysiological and c-Fos study
AU Hassani, O.-K.; Feger, J.
CS Laboratoire de Pharmacologie, Faculte de Pharmacie, Universite R. Descartes, Paris, Fr.
SO Neuroscience (Oxford) (**1999**), 92(2), 533-543
CODEN: NRSCDN; ISSN: 0306-4522
PB Elsevier Science Ltd.
DT Journal
LA English
AB Subthalamic neuronal activity is controlled by a dopaminergic innervation, which may act via D1 and D2 dopamine receptors. This study investigates the effect of apomorphine and the selective D1 and D2 agonists, **SKF 82958** and quinpirole resp., in normal and 6-hydroxydopamine-lesioned rats. The effect of microinjection of these drugs into the subthalamic nucleus was assessed by recording unit activity and the expression of the c-Fos-immunoreactive protein in the subthalamic nucleus. Dopaminergic agonists reduced the discharge rate and did not induce c-Fos expression in the normal rat. Apomorphine and quinpirole increased the discharge rate and induced a strong expression of c-Fos-like immunoreactive proteins, whereas **SKF 82958** induced a decrease of the discharge rate and a slight expression of c-Fos in 6-hydroxydopamine-lesioned rats. The striking contrast in the changes obtained with apomorphine and quinpirole in normal and 6-hydroxydopamine-lesioned rats is discussed in relation to a hyperexpression of D2 dopaminergic receptors on the GABAergic terminals into the subthalamic nucleus. These results show that, in normal rats, dopamine agonists exert an inhibitory control on subthalamic neurons via D1 and D2 receptors. However, in 6-hydroxydopamine-lesioned rats, the hyperactivity of subthalamic neurons is also reduced by D1 receptor agonist but not by D2 dopamine agonists. This last result points out one aspect of the complex mechanisms underlying the physiopathol. of **Parkinson**'s disease.
IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(dopamine receptor agonists effect on subthalamic neuron electrophysiol. and c-Fos in hydroxydopamine-lesioned **Parkinsonism** rat model)
IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(dopamine receptor agonists effect on subthalamic neuron electrophysiol. and c-Fos in hydroxydopamine-lesioned **Parkinsonism** rat model)
RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



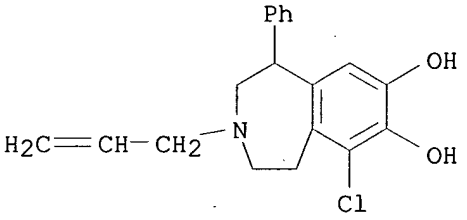
RE.CNT 90 THERE ARE 90 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 22 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1999:349146 HCAPLUS
DN 131:125363
TI Striatal and nigral D1 mechanisms involved in the **antiparkinsonian** effects of **SKF 82958** (APB): studies of tremulous jaw movements in rats
AU Mayorga, A. J.; Trevitt, J. T.; Conlan, A.; Gianutsos, G.; Salamone, J. D.
CS Departments of Psychology and Pharmaceutical Sciences, University of Connecticut, Storrs, CT, 06269-1020, USA
SO Psychopharmacology (Berlin) (**1999**), 143(1), 72-81
CODEN: PSCHDL; ISSN: 0033-3158
PB Springer-Verlag
DT Journal
LA English
AB Previous work has demonstrated that cholinomimetic-induced tremulous jaw movements in rats have temporal and pharmacol. characteristics similar to **parkinsonian** tremor. This rodent model was used to characterize the putative **antiparkinsonian** effects of the full D1 dopamine receptor agonist, **SKF 82958**. Jaw movement activity was induced by the muscarine agonist pilocarpine (4.0 mg/kg IP), and a series of expts. studied the pharmacol. characteristics of the reversal of pilocarpine-induced jaw movements by **SKF 82958**. **SKF 82958** (0.5-2.0 mg/kg IP) reduced the tremulous jaw movements induced by pilocarpine. The suppressive effects of **SKF 82958** on jaw movements were dose-dependently reversed by systemic pretreatment with the selective D1 dopamine receptor antagonist SCH 23390 (0.025-0.2 mg/kg IP); SCH 23390 was about 16 times more potent than the D2 antagonist raclopride at reversing the effects of **SKF 82958**. Intracranial injection of SCH 23390 (0.5-2.0 .mu.g/side) into the ventrolateral striatum, the rodent homolog of the human ventral putamen, dose-dependently reversed the redn. of pilocarpine-induced jaw movements produced by **SKF 82958**. Intracranial injection of SCH 23390 (0.5-2.0 .mu.g/side) into the substantia nigra pars reticulata also dose-dependently reversed the redn. by **SKF 82958** of pilocarpine-induced jaw movements. Injections of SCH 23390 (2.0 .mu.g/side) into control sites dorsal to the striatum or substantia nigra had no effects on the action of **SKF 82958**. Intranigral (SNr) injections of the GABA-A antagonist bicuculline blocked the suppressive effect of systemically administered **SKF 82958** on jaw movement activity. These data suggest that the **antiparkinsonian** actions of **SKF 82958** may be due to stimulation of D1 receptors in the ventrolateral striatum and substantia nigra pars reticulata. In addn., these results indicate that GABA mechanisms in the substantia nigra pars reticulata may be important for the **antiparkinsonian** effects of D1 agonists.
IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)

(striatal and nigral D1 mechanisms involved in **antiparkinsonian** effects of **SKF 82958** in studies of tremulous jaw movements in rats)

IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(striatal and nigral D1 mechanisms involved in **antiparkinsonian** effects of **SKF 82958** in studies of tremulous jaw movements in rats)

RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



RE.CNT 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

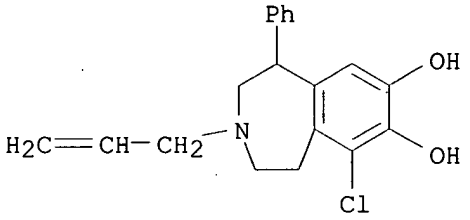
L87 ANSWER 23 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1999:310288 HCAPLUS
DN 131:83335
TI Neurotensin receptors and dopamine transporters: effects of MPTP lesioning and chronic dopaminergic treatments in monkeys
AU Goulet, Martin; Morissette, Marc; Grondin, Richard; Falardeau, Pierre; Bedard, Paul J.; Rostene, William; Di Paolo, Therese
CS Faculty of Pharmacy, Laval University, Quebec, QC, G1K 7P4, Can.
SO Synapse (New York) (**1999**), 32(3), 153-164
CODEN: SYNAET; ISSN: 0887-4476
PB Wiley-Liss, Inc.
DT Journal
LA English
AB The effect of denervation with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) of the dopamine (DA) nigrostriatal pathway on neurotensin (NT) receptor and DA transporter (DAT) in basal ganglia of monkeys (Macaca fascicularis) was investigated. The MPTP lesion induced a marked depletion of DA (90% or more vs. control) in the caudate nucleus and putamen. The densities of NT agonist binding sites labeled with [125I]NT and the NT antagonist binding sites labeled with [3H]SR142948A decreased by half in the caudate-putamen of MPTP-monkeys. In addn., the densities of [125I]NT and [3H]SR142948A binding sites markedly decreased (-77 and -63%, resp.) in the substantia nigra of MPTP-monkeys. Levocabastine did not compete with high affinity for [125I]NT binding in the monkey cingulate cortex, suggesting that only one class of NT receptors was labeled in the monkey brain. An extensive decrease of [3H]GBR12935 DAT binding sites (-92% vs. Control) was obsd. in the striatum of MPTP-monkeys and an important loss of DAT mRNA (-86% vs. Control) was obsd. in substantia nigra. Treatments for 1 mo with either the D1 agonist **SKF-82958** (3 mg/kg/day) or the D2 agonist cabergoline (0.25 mg/kg/day) had no effect on the lesion-induced decrease in NT and DAT binding sites or DAT mRNA levels. The decrease of striatal NT binding sites was less than expected from the decrease of DA content in this nucleus, suggesting only partial localization of NT receptors on nigrostriatal DAergic projections. These data also suggest

that under severe DA denervation, treatment with D1 or D2 DA agonists does not modulate NT receptors and DAT d.

IT **80751-65-1, SKF-82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(under severe dopaminergic denervation treatment with D1 or D2 dopamine receptor agonists does not modulate neurotensin receptors and dopamine transporter d.)

IT **80751-65-1, SKF-82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(under severe dopaminergic denervation treatment with D1 or D2 dopamine receptor agonists does not modulate neurotensin receptors and dopamine transporter d.)

RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



RE.CNT 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 24 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1999:204281 HCAPLUS
DN 131:609
TI Actions of the D1 agonists A-77636 and **A-86929** on locomotion and dyskinesia in MPTP-treated L-dopa-primed common marmosets
AU Pearce, R. K. B.; Jackson, M.; Britton, D. R.; Shiosaki, K.; Jenner, P.; Marsden, C. D.
CS University Department of Clinical Neurology, Institute of Neurology, The National Hospital for Neurology and Neurosurgery, London, WC1N 3BG, UK
SO Psychopharmacology (Berlin) (**1999**), 142(1), 51-60
CODEN: PSCHDL; ISSN: 0033-3158
PB Springer-Verlag
DT Journal
LA English
AB Common marmosets show **parkinsonian** motor deficits following 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administration and develop dyskinesias during chronic L-dopa exposure. The D1 agonists A-77636 [(1R,3S)3-(1'-adamantyl)-1-aminomethyl-3,4-dihydro-5,6-dihydroxy-1H-2-benzopyran.HCl] and **A-86929** [(-)-trans-9,10-hydroxy-2-propyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[c]phenanthrene hydrochloride] possess potent **antiparkinsonian** activity in the MPTP-treated marmoset and the authors now assess their influence on L-dopa-induced dyskinesias. MPTP-treated marmosets with stable motor deficits were treated with L-dopa plus carbidopa for 28 days to induce dyskinesias. Subsequently, they received **A-86929** for 10 days, initially at 0.5 .mu.mol/kg and then at 1.0 .mu.mol/kg for a further 5 days. Several months later, L-dopa 12.5 mg/kg plus carbidopa 12.5 mg/kg was given orally twice daily for 7 days, followed by A-77636 1 .mu.mol/kg for 10 days, and then both A-77636 and L-dopa plus carbidopa were given concurrently for 3 further days. In these L-dopa-primed animals, **A-86929** effectively

reversed akinesia and produced dose-dependent dyskinesias which were significantly less intense than those produced by L-dopa administration. A degree of behavioral tolerance was encountered, but **antiparkinsonian** activity was preserved and elicited behavior was free of hyperkinesis and stereotypy and more naturalistic than that seen with L-dopa. After a week of twice-daily L-dopa dosing, administration of the long-acting D1 agonist A-77636 initially dramatically enhanced locomotion and reproduced dyskinesia with prominent dystonia, but after repeated administration of A-77636, dyskinesia and in particular chorea, gradually disappeared. Tolerance to locomotor stimulation greater than with **A-86929** occurred, although activity remained significantly above baseline levels. There was a marked redn. in L-dopa-induced climbing, stereotypy and hyperkinesis and behavior more closely resembled that of normal unlesioned marmosets. Upon reintroduction of L-dopa concurrently with continued A-77636 administration, dystonic, but virtually no choreic dyskinesias appeared and behavior was once again free of stereotypy and hyperkinesis, contrasting dramatically with the presence of these behaviors along with abundant chorea when L-dopa is given alone. These results show a lesser liability of **A-86929** and A-77636 to reproduce dyskinesia in L-dopa-primed MPTP-lesioned subjects while maintaining effective **antiparkinsonian** activity and producing a more naturalistic motor response. The differential effects of A-77636 on chorea and dystonia, with suppression of chorea and stereotypy on co-administration with L-dopa, may reflect an altered balance of activity in the direct and indirect striatofugal pathways. These results suggest a possible role for D1 agonists in the treatment of **Parkinson**'s disease.

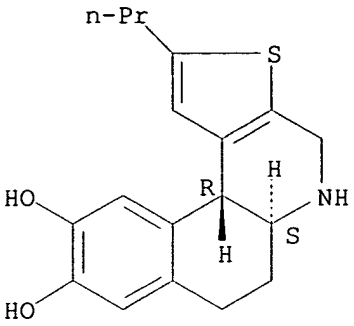
IT **173934-91-3, A-86929**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(actions of D1 agonists A-77636 and **A-86929** on locomotion and dyskinesia in MPTP-treated L-dopa-primed common marmosets in relation to **antiparkinsonian** activity and development of dyskinesia)

IT **173934-91-3, A-86929**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(actions of D1 agonists A-77636 and **A-86929** on locomotion and dyskinesia in MPTP-treated L-dopa-primed common marmosets in relation to **antiparkinsonian** activity and development of dyskinesia)

RN 173934-91-3 HCAPLUS

CN Benzo[f]thieno[2,3-c]quinoline-9,10-diol, 4,5,5a,6,7,11b-hexahydro-2-propyl-, hydrochloride, (5aR,11bS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



● HCl

RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

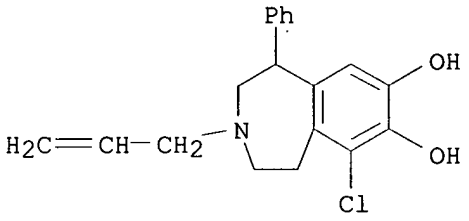
L87 ANSWER 25 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1999:69287 HCAPLUS
DN 130:247309
TI A novel neurotransmitter system involved in the control of motor behavior by the basal ganglia
AU Sanudo-Pena, M. Clara; Walker, Michael
CS Department of Psychology, Brown University, Providence, RI, 02912, USA
SO Annals of the New York Academy of Sciences (**1998**), 860(Neuronal Mechanisms for Generating Locomotor Activity), 475-479
CODEN: ANYAA9; ISSN: 0077-8923
PB New York Academy of Sciences
DT Journal
LA English
AB The aim of the study was to investigate cannabinergic neurotransmitter system in relation to the role of basal ganglia in control of movement. For this, the authors examd. turning behavior following unilateral microinjections of cannabinoids into various basal ganglia structures and the interaction between cannabinoids and dopamine agonists. Also the electrophysiol. effects of cannabinoids at receptors located on the terminals of the striatal efferents to the output nuclei, and the actions of cannabinoid receptors thought to be located on the terminals of the subthalamic nucleus to the output nuclei were examd. Finally in light of the crucial role of dopamine loss in the etiol. of **Parkinson**'s disease the authors employed the 6-OHDA rat model of **Parkinson**'s disease to det. the motor effects of cannabinoid action in the basal ganglia under this pathol. condition. D1 dopamine receptor agonist **SKF82958**, D2 dopamine receptor agonist quinpirole and cannabinoid agonists CP 55940 and WIN 55,212-2, cannabinoid antagonist SR141716A and 6-OHDA were used for these studies. In summary the cannabinoids showed a remarkable modulatory action in the substantia nigra reticulata (SNr) where they act upon both major excitatory and inhibitory inputs. Furthermore cannabinoid agonists oppose the action of dopaminergic drugs acting on both main families of dopamine receptors in the SNr in intact animals but this effect does not occur in animals with dopamine lesions (data not shown). Therefore the authors hypothesize that the inhibitory action of cannabinoids on sub-thalamonigral terminals may be significant for movement disorders that stem from over-activity of the subthalamonigral pathway which includes **Parkinson**'s disease and suggests the potential for a coadjunctive treatment of cannabinoids and dopamine agonists.
IT **80751-65-1, SKF 82958**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(cannabinoid agonist effect on motor behavior control by basal ganglia and interaction between cannabinoids and dopamine agonists in relation to **Parkinsonism** in rat)

IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(cannabinoid agonist effect on motor behavior control by basal ganglia and interaction between cannabinoids and dopamine agonists in relation to **Parkinsonism** in rat)

RN 80751-65-1 HCAPLUS

CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 26 OF 66 HCAPLUS COPYRIGHT 2003 ACS

AN 1999:62850 HCAPLUS

DN 130:232669

TI Differential regulation of striatal preproenkephalin and preprotachykinin mRNA levels in MPTP-lesioned monkeys chronically treated with dopamine D1 or D2 receptor agonists

AU Morissette, Marc; Grondin, Richard; Goulet, Martin; Bedard, Paul J.; Di Paolo, Therese

CS Centre de Recherches en Endocrinologie Moleculaire, Le Centre Hospitalier Universitaire de Quebec, Quebec, QC, G1V 4G2, Can.

SO Journal of Neurochemistry (**1999**), 72(2), 682-692
CODEN: JONRA9; ISSN: 0022-3042

PB Lippincott Williams & Wilkins

DT Journal

LA English

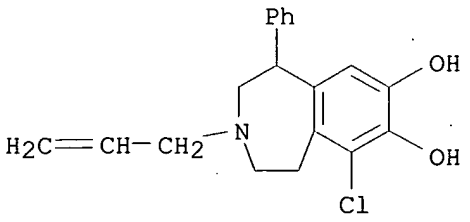
AB Studies in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned monkeys and in **parkinsonian** patients show elevated preproenkephalin (PPE) mRNA levels, unaltered by chronic L-DOPA therapy, whereas preprotachykinin (PPT) mRNA levels are decreased by the lesion and cor. by L-DOPA. The relative contributions of the dopamine D1 and D2 receptors for PPE mRNA regulation were investigated in the present study and compared with those for PPT mRNA. In situ hybridization was used to measure peptide mRNA levels in the striatum of MPTP cynomolgus monkeys after chronic 1-mo treatment with the D1 agonist **SKF-82958**, administered s.c. in pulsatile or continuous mode, compared with the long-acting D2 agonist cabergoline. Normal as well as untreated MPTP animals were also studied. PPE mRNA levels were elevated in the caudate nucleus and putamen of untreated MPTP monkeys compared with control animals with a more pronounced increase in the lateral as compared with the medial part of both structures. PPT mRNA levels showed a rostrocaudal gradient, with higher values in the middle of the caudate-putamen and more so in the medial vs. the lateral parts. PPT mRNA levels were decreased in the caudate and putamen of untreated MPTP monkeys compared with control animals, and this was obsd. in the middle and

posterior parts of these brain areas. Elevated PPE and decreased PPT mRNA levels obsd. after MPTP exposure were cor. after treatment with cabergoline (0.25 mg/kg, every other day), a dose that had **antiparkinsonian** effects and did not give sustained dyskinesia. In contrast, elevated PPE mRNA levels obsd. in untreated MPTP monkeys were markedly increased by pulsatile administration of **SKF-82958** (1 mg/kg, three times daily) in two monkeys in which the **parkinsonian** symptoms were improved and dyskinesias developed, whereas it remained close to control values in a third one that did not display dyskinesias despite a sustained improvement in disability; a shorter duration of motor benefit (wearing off) over time was obsd. in these three animals. By contrast, pulsatile administration of **SKF-82958** cor. the decreased PPT level obsd. in untreated MPTP monkeys. Continuous treatment with **SKF-82958** (equiv. daily dose) produced no clear **antiparkinsonian** and dyskinetic responses and did not alter the denervation-induced elevation of PPE or decrease of PPT mRNA levels. The present data suggest an opposite contribution of the dopamine D1 receptors (stimulatory) as compared with the dopamine D2 receptors (inhibitory) on PPE mRNA, whereas a similar stimulatory contribution of D1 or D2 receptors is obsd. for PPT mRNA. An increase in PPE expression could be involved in the induction of dyskinesias and wearing off, whereas the authors' data do not support this link for PPT. The **antiparkinsonian** response was assocd. with a correction of the lesion-induced decrease of PPT.

IT **80751-65-1, SKF-82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(differential regulation of striatal preproenkephalin and preprotachykinin mRNA levels in MPTP-lesioned monkeys chronically treated with dopamine D1 or D2 receptor agonists)

IT **80751-65-1, SKF-82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(differential regulation of striatal preproenkephalin and preprotachykinin mRNA levels in MPTP-lesioned monkeys chronically treated with dopamine D1 or D2 receptor agonists)

RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)

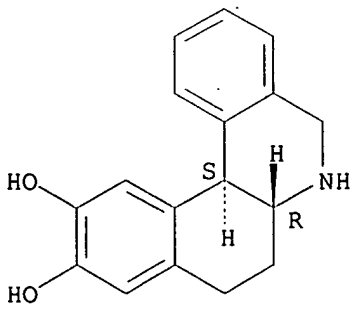


RE.CNT 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 27 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1999:5739 HCAPLUS
DN 130:205015
TI Effects of the full dopamine D1 receptor agonist **dihydrexidine** in **parkinson**'s disease
AU Blanchet, Pierre J.; Fang, John; Gillespie, Marjorie; Sabounjian, LuAnn; Locke, Kenneth W.; Gammans, Richard; Mouradian, M. Maral; Chase, Thomas N.
CS Experimental Therapeutics Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD,

20892-1406, USA
SO Clinical Neuropharmacology (**1998**), 21(6), 339-343
CODEN: CLNEDB; ISSN: 0362-5664
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB The contribution of dopamine D1 receptor stimulation to the motor effects of dopaminergic drugs in patients with **Parkinson**'s disease remains undetd. The authors of this article studied the clin. efficacy, pharmacokinetics, and tolerability of the full D1 receptor agonist **dihydrexidine**, (.+-.)-trans-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[a] phenanthridine hydrochloride in a double-blind, placebo-controlled trial in four patients with **Parkinson**'s disease. Single i.v. doses were carefully titrated according to a fixed schedule ranging from 2 mg to the highest tolerated dose (or a max. of 70 mg) infused over either 15 or 120 min. The only patient to achieve a plasma drug concn. greater than 100 ng/mL had a brief but definite motor improvement accompanied by choreic dyskinesias similar to the response to levodopa. Dose-limiting adverse effects, including flushing, hypotension, and tachycardia, were obsd. in all cases, esp. with rapid infusions. No nausea or emesis occurred. Pharmacokinetic studies yielded a plasma half-life <5 min. These preliminary data suggest that **dihydrexidine** has a marginal therapeutic window for providing an anti-**parkinsonian** effect, although it remains uncertain how much of this effect is attributable to pure D1 receptor stimulation.
IT **123039-93-0, Dihydrexidine**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); OCCU (Occurrence); PROC (Process);
USES (Uses)
(dopamine D1 receptor agonist **dihydrexidine** effect in **parkinson**'s disease in humans)
IT **123039-93-0, Dihydrexidine**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); OCCU (Occurrence); PROC (Process);
USES (Uses)
(dopamine D1 receptor agonist **dihydrexidine** effect in **parkinson**'s disease in humans)
RN 123039-93-0 HCAPLUS
CN Benzo[a]phenanthridine-10,11-diol, 5,6,6a,7,8,12b-hexahydro-, (6aR,12bS)-rel- (9CI) (CA INDEX NAME)

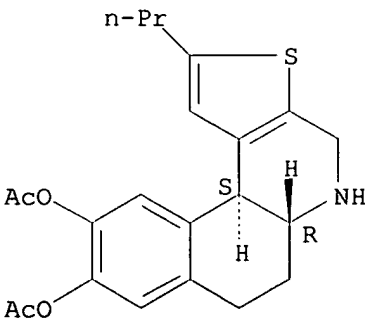
Relative stereochemistry.



RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 28 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1998:633420 HCAPLUS
DN 130:46932
TI Efficacy of dopamine D1 receptor agonists **A-86929** and ABT-431 in animal models of **Parkinson**'s disease
AU Shiosaki, Kazumi; Asin, Karen E.; Bedard, Paul; Britton, Donald R.; Jenner, Peter; Lin, Chun Wei; Michaelides, Michael; Williams, Michael
CS Pharmaceutical Products Division, Abbott Laboratories, Neurological and Urological Diseases Research, Abbott Park, IL, 60064-3500, USA
SO Biomedical and Health Research (**1998**), 19(Dopamine Receptor Subtypes), 84-97
CODEN: BIHREN; ISSN: 0929-6743
PB IOS Press
DT Journal; General Review
LA English
AB A review, with 32 refs. The in vitro pharmacol. profile for **A-86929** and the behavioral properties of **A-86929** and ANT-431 in rodent and primate models of **Parkinson**'s disease are discussed. The evidence suggests that **A-86929** and ABT-431 may be effective in the long-term treatment of **Parkinson**'s disease, with advantage, relative to L-Dopa, of reduced liability to induce dyskinesia.
IT **166591-11-3**, ABT-431 **173934-91-3**, **A-86929**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(efficacy of dopamine D1 receptor agonists **A-86929** and ABT-431 in animal models of **Parkinson**'s disease)
IT **166591-11-3**, ABT-431
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(efficacy of dopamine D1 receptor agonists **A-86929** and ABT-431 in animal models of **Parkinson**'s disease)
RN 166591-11-3 HCAPLUS
CN Benzo[f]thieno[2,3-c]quinoline-9,10-diol, 4,5,5a,6,7,11b-hexahydro-2-propyl-, diacetate (ester), hydrochloride, (5aR,11bS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



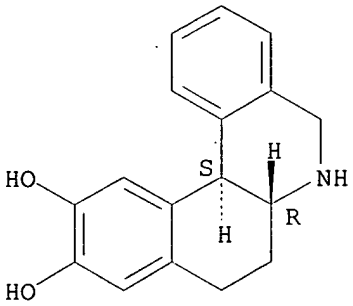
HCl

RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 29 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1998:633418 HCAPLUS
DN 130:46931
TI Functional effects of novel dopamine ligands: **dihydrexidine** and **parkinson**'s disease as a first step
AU **Mailman, Richard B.**; Lawler, Cindy P.; Lewis, Mechelle M.; Blake, Bonnie; **Nichols, David E.**
CS Neuroscience Center, Departments of Pharmacology, Psychiatry, and Medicinal Chemistry, University of North Carolina School of Medicine, Chapel Hill, NC, 27599-7250, USA
SO Biomedical and Health Research (**1998**), 19(Dopamine Receptor Subtypes), 64-83
CODEN: BIHREN; ISSN: 0929-6743
PB IOS Press
DT Journal; General Review
LA English
AB A review, with 106 refs. While there has been a major focus on the design of new dopaminergic ligands that have selectivity for receptor isoforms, the functional characteristics of new or existing drugs often have been neglected. We have sought to understand the mol. basis for agonism vs. antagonism at the dopamine D1 receptor, and in the process, developed the first high affinity, full D1 agonist, **dihydrexidine**. We had hypothesized that full D1 agonists would have profound **antiparkinsonian** effects, and **dihydrexidine** permitted this idea to be tested in MPTP-lesioned African Green Monkeys. **Dihydrexidine** caused almost complete elimination of all **parkinsonian** signs, demonstrating for the first time the important role of D1 receptors in pharmacotherapy of **Parkinson**'s disease. Other evidence suggests that full D1 agonists like **dihydrexidine** also may have utility in improving other CNS functions in which D1 receptors play an important role. The long-term use of these drugs, however, may require other properties to be engineered into the drugs, for example, concomitant D2 activation (as is seen with **dihydrexidine**). It is now accepted that a single receptor isoform can couple to a no. of G-proteins (making it possible for a ligand that binds-to a single receptor type to encounter, and "select", among multiple G-protein subtypes). Yet studies with **dihydrexidine** and its analogs have led to the formulation of the "functional selectivity" hypothesis, an idea based on the concept that drugs themselves can cause functional multiplicity even when interacting with a single receptor isoform. The foundation of this hypothesis is extensive data showing that some drugs (like **dihydrexidine**) can bind to a single receptor isoform, yet cause distinct functional changes depending on the cellular localization of the receptor-G protein complex. Thus, in D2 systems, **dihydrexidine** has both agonist properties (e.g., in inhibiting adenylate cyclase) and antagonist properties (not inhibiting dopamine release). One mechanism for functional selectivity may be atypical (compared to dopamine) conformation changes induced when such drugs bind to the receptor-G protein complex. These distinct conformation changes force the dissocn. of some, but not all, receptor-G-protein complexes (depending on the G-protein to which the receptor is coupled). The particular type(s) of G-protein are dependent on both the type of cell, and the location in the cell, where the receptor of interest is located. Such functional targeting allows drug effects to be refined to a degree not possible just by targeting specific receptor isoforms. This could yield important therapeutic advances, although it introduces a new level of complexity that will require significantly greater understanding of receptor dynamics and the interaction with transduction mechanisms.
IT **123039-93-0, Dihydrexidine**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(functional effects of dopamine D1 receptor ligand

dihydrexidine in **parkinsonism**)
IT **123039-93-0, Dihydrexidine**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(functional effects of dopamine D1 receptor ligand **dihydrexidine** in **parkinsonism**)
RN 123039-93-0 HCAPLUS
CN Benzo[a]phenanthridine-10,11-diol, 5,6,6a,7,8,12b-hexahydro-, (6aR,12bS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



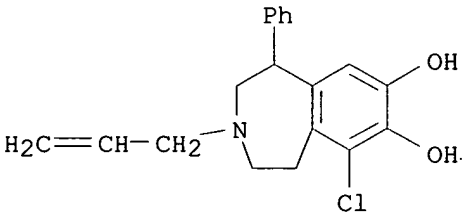
RE.CNT 106 THERE ARE 106 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 30 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1998:53485 HCAPLUS
DN 128:200889
TI Trihexyphenidyl interactions with the dopamine D1-selective receptor agonist **SKF-82958** and the D2-selective receptor agonist N-0923 in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced **hemiparkinsonian** monkeys
AU Domino, Edward F.; Ni, Lisong
CS Department of Pharmacology, University of Michigan, Ann Arbor, MI, USA
SO Journal of Pharmacology and Experimental Therapeutics (**1998**), 284(1), 307-311
CODEN: JPETAB; ISSN: 0022-3565
PB Williams & Wilkins
DT Journal
LA English
AB The effects of the **antiparkinsonian** agent trihexyphenidyl, a selective M1 muscarinic cholinergic receptor antagonist, were studied in doses of 100, 320 and 1000 .mu.g/kg i.m. alone. Trihexyphenidyl was then studied in combination with the selective dopamine receptor D1 agonist **SKF-82958** [(.+-.)-6-chloro-7-8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-benzazepine hydrobromide] and the selective D2 agonist N-0923 [(-)2-(N-propyl-N-2-thienylethyl)amino-5-hydroxytetralin HCl] on rotational behavior in five 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned **hemiparkinsonian** monkeys. Given alone, trihexyphenidyl had no effect on ipsiversive and slightly enhanced contraversive circling. Contraversive circling produced by 74.8 and 234 .mu.g/kg **SKF-82958** i.m. was potentiated by increasing doses of trihexyphenidyl. Contraversive circling produced by 10 and 32 .mu.g/kg N-0923 i.m. was progressively reduced with increasing doses of trihexyphenidyl. The results obtained indicate differential actions on circling behavior between a selective M1 muscarinic cholinergic receptor antagonist and selective D1 and D2 receptor agonists in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine monkey model of **hemiparkinsonism**.

IT **80751-65-1, SKF-82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(trihexyphenidyl interactions with dopamine D1 receptor agonist **SKF-82958** and D2 receptor agonist N-0923 in methylphenyltetrahydropyridine-induced **hemiparkinsonian** monkeys in relation to effect on circling behavior)

IT **80751-65-1, SKF-82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(trihexyphenidyl interactions with dopamine D1 receptor agonist **SKF-82958** and D2 receptor agonist N-0923 in methylphenyltetrahydropyridine-induced **hemiparkinsonian** monkeys in relation to effect on circling behavior)

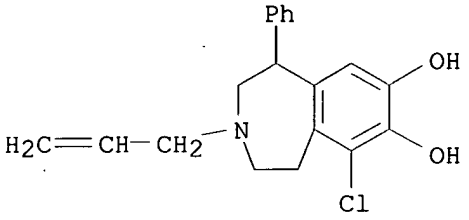
RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 31 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1997:712677 HCAPLUS
DN 128:10246
TI Dopamine receptor subtypes as targets for the pharmacotherapy of **Parkinson**'s disease
AU Andringa, G.; Vermeulen, R. J.; Drukarch, B.; Stoof, J. C.; Cools, A. R.
CS Dep. Neurol., Res. Inst. Neuroscis., Vrjie Univ., Amsterdam, Neth.
SO Advances in Pharmacology (San Diego) (**1998**), 42(Catecholamines), 792-795
CODEN: ADPHEL; ISSN: 1054-3589
PB Academic
DT Journal
LA English
AB The therapeutic and unwanted side effects of two D1 agonists, SKF 81297 and **SKF 82958**, were evaluated in the primate model of **Parkinson**'s disease. SKF 81297 and **SKF 82958** "stimulate" to a certain extent motor behavior, but they lack a clear effect on goal-directed movements, which might be considered a real **antiparkinsonian** effect. Both agonists induce dyskinetic effects and epileptoid activity. Thus, a serious doubts were raised concerning whether pursuing behavioral studies with these SKF analogs in monkeys, aiming at the development of new **antiparkinsonian** drugs, is a fruitful endeavor. The in vitro expts. with SKF 83959 are also discussed.
IT **80751-65-1, SKF 82958**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(dopamine receptor subtypes as targets for pharmacotherapy of **Parkinson**'s disease)

IT **80751-65-1, SKF 82958**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(dopamine receptor subtypes as targets for pharmacotherapy of **Parkinson**'s disease)
RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



L87 ANSWER 32 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1997:605133 HCAPLUS
DN 127:257518
TI Potential therapeutic use of the selective dopamine D1 receptor agonist, **A-86929**: an acute study in **parkinsonian** levodopa-primed monkeys
AU Grondin, Richard; Bedard, Paul J.; Britton, Donald R.; Shiosaki, Kazumi
CS Department of Pharmacology, Faculty of Medecine, Hopital de l'Enfant-Jesus, Laval University and Centre de Recherche en Neurobiologie, QC, G1J 1Z4, Can.
SO Neurology (**1997**), 49(2), 421-426
CODEN: NEURAI; ISSN: 0028-3878
PB Lippincott-Raven
DT Journal
LA English
AB The clin. utility of dopamine (DA) D1 receptor agonists in the treatment of **Parkinson**'s disease (PD) is still unclear. The therapeutic use of selective DA D1 receptor agonists such as **SKF-82958** and A-77636 seems limited because of their duration of action, which is too short for **SKF-82958** (<1 h) and too long for A-77636 (>20 h, leading to behavioral tolerance). We therefore conducted the present acute dose-response study in four 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-exposed cynomolgus monkeys primed to exhibit levodopa-induced dyskinesias to evaluate the locomotor and dyskinetic effects on challenge with four doses (from 0.03 to 1.0 mg/kg) of **A-86929**, a selective and full DA D1-like receptor agonist with an intermediate duration of action. Levodopa and the DA D2-like receptor agonist, LY-171555 were also used for comparison. Acute administration of **A-86929** was as efficacious in alleviating MPTP-induced **parkinsonism** as levodopa and LY-171555, but was less likely to reproduce the levodopa-induced dyskinesias in these animals than with either LY-171555 or subsequent challenge of levodopa. Selective stimulation of the DA D1 receptor may provide better integration of neural inputs transmitted to the internal segment of the globus pallidus (referred to as the basal ganglia output) compared with levodopa and selective DA D2 receptor agonists. Potent DA D1 receptor agents with an intermediate duration of efficacy such as **A-86929** (approx. 4 h at higher doses tested) are potential therapeutic tools in PD and merit further attention.
IT **173934-91-3, A-86929**:
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

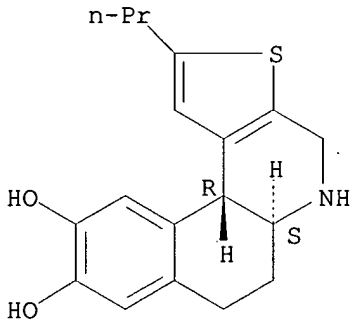
study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(potential therapeutic use of dopamine D1 receptor agonist, **A-86929**: study in **parkinsonian** levodopa-primed monkeys)

IT **173934-91-3, A-86929:**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(potential therapeutic use of dopamine D1 receptor agonist, **A-86929**: study in **parkinsonian** levodopa-primed monkeys)

RN 173934-91-3 HCAPLUS

CN Benzo[f]thieno[2,3-c]quinoline-9,10-diol, 4,5,5a,6,7,11b-hexahydro-2-propyl-, hydrochloride, (5aR,11bS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



● HCl

L87 ANSWER 33 OF 66 HCAPLUS COPYRIGHT 2003 ACS

AN 1997:585170 HCAPLUS

DN 127:257475

TI D1 agonist **dihydrexidine** releases acetylcholine and improves cognitive performance in rats

AU Steele, Thomas D.; Hodges, Donald B., Jr.; Levesque, Tamara R.; Locke, Kenneth W.

CS Interneuron Pharmaceuticals Inc., Lexington, MA, 02173, USA

SO Pharmacology, Biochemistry and Behavior (**1997**), 58(2), 477-483
CODEN: PBBHAU; ISSN: 0091-3057

PB Elsevier

DT Journal

LA English

AB **Dihydrexidine** is a selective, full-efficacy dopamine D1 receptor agonist that has displayed therapeutic potential in **Parkinson's** disease by reversing motor deficits of MPTP-treated monkeys. The present study monitored the effects of **dihydrexidine** on acetylcholine release in rat brain by using in vivo microdialysis. Moderate doses of **dihydrexidine** [3 and 10 mg/kg, i.p. (IP)] elevated extracellular concns. of acetylcholine by 40-60% in rat striatum; higher doses did not significantly alter acetylcholine release. SCH 23390 blocked the **dihydrexidine**-induced increase, indicating a D1 receptor-mediated action. A more robust stimulatory effect of **dihydrexidine** on acetylcholine release was obsd. in prefrontal cortex (to 300% of basal output) than in striatum. **Dihydrexidine** was also evaluated in a passive avoidance procedure in rats to det. if its neurochem. effects

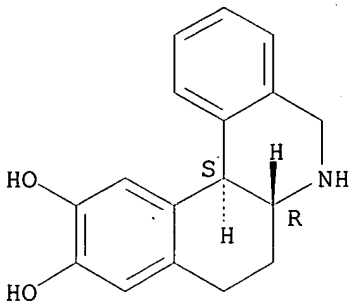
translated into cognition-enhancing activity; in this assay, **dihydrexidine** (0.3 mg/kg, IP) significantly improved the scopolamine-induced deficits. The results of these studies suggest that the acetylcholine-releasing properties of **dihydrexidine** and other D1 agonists may underlie their cognition-enhancing activity and thus may have clin. value in the treatment of dementia.

IT **123039-93-0, Dihydrexidine**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(D1 agonist **dihydrexidine** releases acetylcholine and improves cognitive performance)

IT **123039-93-0, Dihydrexidine**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(D1 agonist **dihydrexidine** releases acetylcholine and improves cognitive performance)

RN 123039-93-0 HCAPLUS
CN Benzo[a]phenanthridine-10,11-diol, 5,6,6a,7,8,12b-hexahydro-, (6aR,12bS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



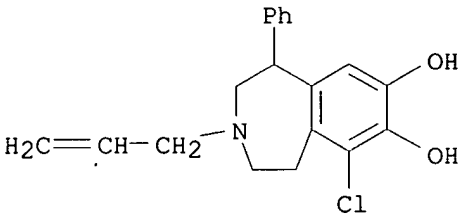
L87 ANSWER 34 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1997:582744 HCAPLUS
DN 127:243162
TI Differential therapeutic effects of dopamine D1 and D2 agonists in MPTP-induced **parkinsonian** monkeys: clinical implications
AU Kuno, Sadako
CS Department of Neurology, Center for Neurological Diseases, Utano National Hospital, Narutaki, 616, Japan
SO European Neurology (**1997**), 38(Suppl. 1), 18-22
CODEN: EUNEAP; ISSN: 0014-3022
PB Karger
DT Journal
LA English
AB L-DOPA, the precursor of dopamine, remains most effective in the treatment of patients with **Parkinson**'s disease, but prolonged L-DOPA treatment often produces adverse effects, including dyskinesia and psychosis. Dopamine receptors can be divided into two major subtypes, D1 and D2. Might both subtypes of the dopamine receptor be equally relevant to amelioration of **parkinsonian** symptoms and responsible for the adverse side effects. To address this question, the effects of D1 or D2 receptor agonists alone and in joint administration were examd. in MPTP-induced **parkinsonian** monkeys. The **parkinsonian** symptoms, such as tremor, bradykinesia and rigidity, and the adverse side effects, such as hyperactivity and aggressiveness, were evaluated independently using different behavioral criteria. The results showed

that **antiparkinsonian** effects can be exerted either by the D1 agonist (**SKF 82958**) alone or by the D2 agonist (quinpirole) alone, whereas hyperactivity and aggressiveness manifested by dopamine agonists require coactivation of the D1 and D2 receptors. Thus, the **antiparkinsonian** effect can be dissocd. from the adverse effect by therapeutic strategy. It is implied that imbalances in activation of the D1 and D2 receptors may provide a favorable approach for long-term treatment of **parkinsonian** patients with dopamine drugs.

IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(differential therapeutic effects of dopamine D1 and D2 agonists in MPTP-induced **parkinsonian** monkeys)

IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(differential therapeutic effects of dopamine D1 and D2 agonists in MPTP-induced **parkinsonian** monkeys)

RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



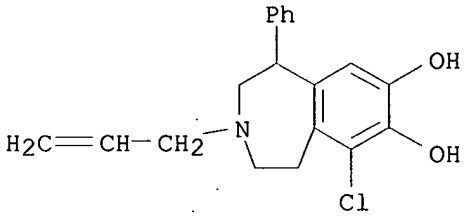
L87 ANSWER 35 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1997:438193 HCAPLUS
DN 127:60212
TI Selective full dopamine D1-like (**SKF-82958**) and D2-like (N-0923) agonist combination in the MPTP monkey model of **hemiparkinsonism**
AU Domino, Edward F.
CS Department of Pharmacology, University of Michigan, A200E MSRBIII, Ann Arbor, MI, 48109-0632, USA
SO Brain Research Bulletin (**1997**), 43(1), 93-95
CODEN: BRBUDU; ISSN: 0361-9230
PB Elsevier
DT Journal
LA English
AB Both **SKF-82958** and N-0923, selective full D1-like and D2-like agonists, resp., given i.m. produced contraversive circling and reduced neurol. deficits in monkeys with MPTP (1,2,3,6-tetrahydro-1-methyl-4-phenylpyridine)-induced **hemiparkinsonism**. A small fixed dose of N-0923 (10 .mu.g/kg) and increasing doses of **SKF-82958** (23.4-234 .mu.g/kg) in combination were synergistic or antagonistic in this animal model. A small dose (23.4 .mu.g/kg) of **SKF-82958**, in combination with N-0923, caused potentiation, an intermediate dose (74.8 .mu.g/kg) in combination produced additive effects, while a very large dose (234 .mu.g/kg) in combination produced antagonism. All 3 doses of **SKF-82958** prolonged the duration of action of a small dose (10 ng/kg) of N-0923. Selective D1-like and D2-like agonists should be studied as potential therapeutic agents alone and in combination in human idiopathic

parkinsonism, esp. using low and intermediate doses.

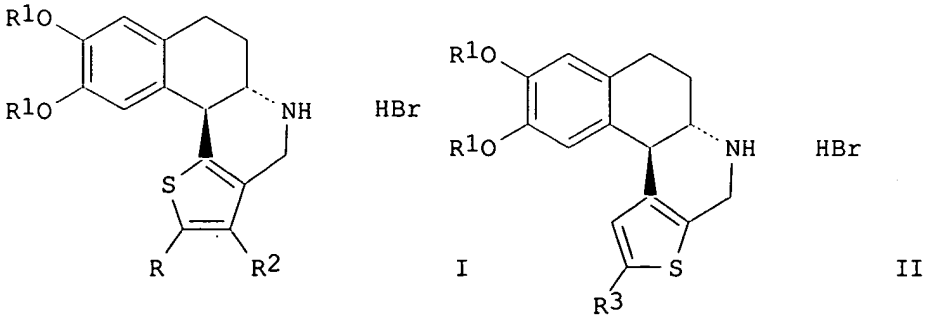
IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(dopamine D1 (**SKF-82958**) and D2 (N-0923) agonist combination effect in **parkinsonism** model)

IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(dopamine D1 (**SKF-82958**) and D2 (N-0923) agonist combination effect in **parkinsonism** model)

RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



L87 ANSWER 36 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1997:310077 HCAPLUS
DN 127:5027
TI Substituted Hexahydrobenzo[f]thieno[c]quinolines as Dopamine D1-Selective Agonists: Synthesis and Biological Evaluation in Vitro and in Vivo
AU Michaelides, Michael R.; Hong, Yufeng; DiDomenico, Stanley, Jr.; Bayburt, Erol K.; Asin, Karen E.; Britton, Donald R.; Lin, Chun Wei; Shiosaki, Kazumi
CS Neuroscience Research Pharmaceutical Discovery, Abbott Laboratories, Abbott Park, IL, 60064-3500, USA
SO Journal of Medicinal Chemistry (**1997**), 40(11), 1585-1599
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
GI



AB A series of substituted 9,10-dihydroxyhexahydrobenzo[f]thieno[c]quinolines I (R = H, Me, Et, Pr, Bu, n-hexyl, cyclohexyl, CH2cyclopentyl, Cl; R1 = H,

Me; R2 = H, Pr), varying with respect to the position of the thiophene relative to the benzo[f]quinoline core and the nature and position of the substituent on the thiophene, were prepd. and evaluated for their affinity and selectivity for the dopamine D1-like receptor. The thieno regioisomers II (R3 = H, Me, Et, Pr, Bu, n-pentyl, CMe3, CHMe2, CH2CHMe2, CH2CH2CHMe2, cyclohexyl, Ph, 3-MeC6H4, Cl) bearing a small alkyl (C1-C3) substituent at the 2 position were potent (Ki < 20 nM) and selective (D2/D1 > 50) D1 agonists with close to full agonist activity (IA > 85%). The compds. were resolved and found to exhibit a high level of enantiospecificity in their interaction with the D1 receptor. Selected compds. were tested in vivo in the 6-OHDA rodent model of **Parkinson**'s disease and for their liability to produce seizure-like activities in mice. (5AR)-trans-2-Propyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[c]phenanthrene-9,10-diol emerged as the compd. with the best overall in vivo profile in terms of potency (ED50 = 0.04 .mu.mol/kg) and safety.

IT **166590-61-0P 166590-73-4P 166590-74-5P**
166590-75-6P 166590-76-7P 166590-77-8P
166590-92-7P 166590-93-8P 187660-89-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of)

IT **166590-62-1P 166590-63-2P 166590-64-3P**
166590-65-4P 166590-66-5P 166590-67-6P
166590-68-7P 166590-71-2P 166590-72-3P
166590-78-9P 166590-82-5P 166590-83-6P
166590-84-7P 166590-85-8P 166590-96-1P
166590-97-2P 173934-91-3P 187660-85-1P
187660-92-0P 187660-95-3P 190076-78-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis and biol. evaluation in vitro and in vivo of substituted hexahydrobenzo[f]thieno[c]quinolines as dopamine D1-selective agonists)

IT **166591-26-0P 166591-30-6P**
RL: PUR (Purification or recovery); SPN (Synthetic preparation); PREP (Preparation)
(synthesis and biol. evaluation in vitro and in vivo of substituted hexahydrobenzo[f]thieno[c]quinolines as dopamine D1-selective agonists)

IT **39251-22-4 65601-86-7 166591-21-5**
166591-29-3 166591-48-6 166591-52-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis and biol. evaluation in vitro and in vivo of substituted hexahydrobenzo[f]thieno[c]quinolines as dopamine D1-selective agonists)

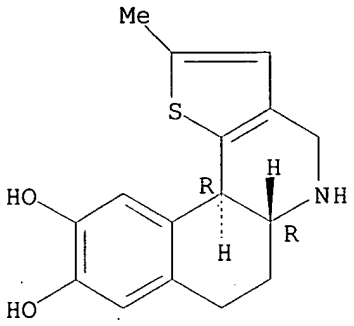
IT **35491-96-4P 73540-75-7P 166591-12-4P**
166591-13-5P 166591-14-6P 166591-15-7P
166591-16-8P 166591-19-1P 166591-31-7P
166591-32-8P 166591-50-0P 166591-55-5P
166591-57-7P 166591-63-5P 171482-82-9P
187660-99-7P 187661-00-3P 187661-09-2P
187661-10-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and biol. evaluation in vitro and in vivo of substituted hexahydrobenzo[f]thieno[c]quinolines as dopamine D1-selective agonists)

IT **166590-61-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of)

RN 166590-61-0 HCAPLUS
CN Benzo[f]thieno[3,2-c]quinoline-9,10-diol, 4,5,5a,6,7,11b-hexahydro-2-

methyl-, hydrobromide, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



● HBr

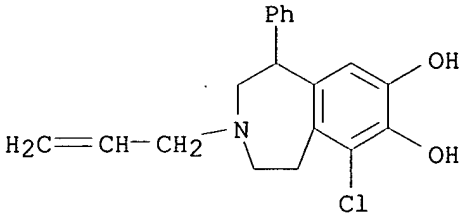
L87 ANSWER 37 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1997:273324 HCAPLUS
DN 126:338764
TI Talipexole or pramipexole combinations with chloro-APB (**SKF 82958**) in MPTP-induced **hemiparkinsonian** monkeys
AU Domino, Edward F.; Ni, Lisong; Zhang, Huilei; Kohno, Yasuko; Sasa, Masashi
CS Department of Pharmacology, A220E MSRBIII, University of Michigan, Ann Arbor, MI, 48109-0632, USA
SO European Journal of Pharmacology (**1997**), 325(2/3), 137-144
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier
DT Journal
LA English
AB The effects of two predominant dopamine D2-like receptor agonists, talipexole (6-allyl-2-amino-5,6,7,8-tetrahydro-4H-thiazolo [4,5-d]-azepine dihydrochloride, B-HT 920 CL2) and pramipexole (S(-)2-amino-4,5,6,7-tetrahydro-6-propyl-aminobenzothiazole dihydrochloride, SND 919 CL2Y), were studied alone and in combination with the selective dopamine D1-like receptor agonist chloro-APB ((.+-.)6-chloro-7-8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-benzazepine hydrobromide, **SKF 82958**) in five chronic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lesioned **hemiparkinsonian** monkeys. Talipexole induced contraversive rotation in a dose-dependent manner up to 32 .mu.g/kg, i.m. Talipexole was more potent than pramipexole (10 vs. 32 .mu.g/kg, i.m.), but pramipexole was more efficacious in producing contraversive rotational behavior and significant hand movements in the afflicted limb. Larger doses of chloro-APB also produced contraversive rotation. Combinations of each dopamine D2-like receptor agonist in a median ED with chloro-APB (23.4 and 74.8 .mu.g/kg, i.m.) had synergistic effects, producing either addn. or potentiation, depending upon the dose used. The effects noted with these combinations were less than the effect of a large dose (100 .mu.g/kg) of pramipexole. Talipexole, in the largest dose studied (100 .mu.g/kg, i.m.), produced sedation which was not seen with the same dose of pramipexole. No significant extrapyramidal side effects were noted with either agent.
IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(**antiparkinsonian** effect of combination of dopamine D2- and

D1-like receptor agonists talipexole, pramipexole, and **SKF 82958**)

IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(**antiparkinsonian** effect of combination of dopamine D2- and D1-like receptor agonists talipexole, pramipexole, and **SKF 82958**)

RN 80751-65-1 HCAPLUS

CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



L87 ANSWER 38 OF 66 HCAPLUS COPYRIGHT 2003 ACS

AN 1997:270840 HCAPLUS

DN 126:325416

TI The selective dopamine D1 receptor agonist **A-86929** maintains efficacy with repeated treatment in rodent and primate models of **Parkinson**'s disease

AU Asin, K. E.; Domino, E. F.; Nikkel, A.; Shiosaki, K.

CS Neuroscience Research Division, Abbott Labs., Abbott Park, IL, 60064-3500, USA

SO Journal of Pharmacology and Experimental Therapeutics (**1997**), 281(1), 454-459
CODEN: JPETAB; ISSN: 0022-3565

PB Williams & Wilkins

DT Journal

LA English

AB The ability of the selective dopamine D1 receptor agonist (5aR, 11bS)-4,5,5a,6,7,11b-hexahydro-2-propyl-3-thia-5-azacyclopent-1-ena[c]-phenanthrene-9,10-diol (**A-86929**) to induce contralateral rotation after repeated administration was detd. in rodent and primate models of **Parkinson**'s disease. Testing was conduced in rats previously given unilateral 6-hydroxydopamine injections and in macaques previously given unilateral, intracarotid infusions of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Both treatments have been shown to reduce forebrain dopamine levels on the side of the infusion. Such animals rotate contralaterally after injections of direct-acting dopamine receptor agonists. Rats were administered **A-86929** (0.11 or 0.22 .mu.mol/kg s.c.) three times daily for 10 days, with injections spaced 3 h apart, and rotation was measured across a 9-h period on various treatment days. Initially, monkeys were given various doses of **A-86929** (0.03, 0.10 or 0.30 .mu.mol/kg i.m.), and rotation was monitored for 3 h after each dose. Significant, dose-dependent levels of contralateral rotation were achieved. Monkeys were next treated three times daily at 3-h intervals with **A-86929** (0.3 .mu.mol/kg). Anal. of total, daily rotation scores indicated that the magnitude of the behavioral response did not change significantly across the 10-day treatment period in monkeys, although it increased in rats (0.22 .mu.mol/kg). The first daily injection tended to elicit greater and longer-lived responses that the

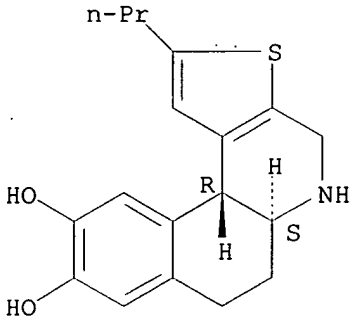
subsequent daily injections in both species. In monkeys, this was particularly true on the first test a day and was not seen by the last test. This study suggests that a selective D1 receptor agonist, such as **A-86929**, with full intrinsic activity relative to dopamine, may be useful for the treatment of **Parkinson**'s disease.

IT **173934-91-3, A-86929**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(dopamine D1 receptor agonist **A-86929** maintains **antiparkinsonian** activity after repeated treatment)

IT **173934-91-3, A-86929**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(dopamine D1 receptor agonist **A-86929** maintains **antiparkinsonian** activity after repeated treatment)

RN 173934-91-3 HCAPLUS
CN Benzo[f]thieno[2,3-c]quinoline-9,10-diol, 4,5,5a,6,7,11b-hexahydro-2-propyl-, hydrochloride, (5aR,11bS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



● HCl

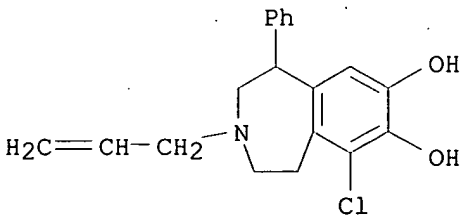
L87 ANSWER 39 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1996:459367 HCAPLUS
DN 125:158360
TI Dopamine D1 receptor desensitization profile in MPTP-lesioned primates
AU Blanchet, Pierre J.; Grondin, Richard; Bedard, Paul J.; Shiosaki, Kazumi; Britton, Donald R.
CS Neurobiology Research Centre, Hopital de l'Enfant-Jesus, Quebec City, Can.
SO European Journal of Pharmacology (**1996**), 309(1), 13-20
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier
DT Journal
LA English
AB The motor effects of dopamine D1 receptor activation and the optimal way to stimulate these receptors were studied in a primate model of **parkinsonism** induced by the neurotoxin 1-methyl-4-phenyl-1,2,3,6 -tetrahydropyridine (MPTP), using 2 selective full dopamine D1 receptor agonists: A-77636 ([1R,3S] 3-(1'-adamantyl)-1-aminomethyl-3,4 -dihydro-5,6-dihydroxy-1H-2-benzopyran hydrochloride), and **SKF 82958** (6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H -3-benzazepine hydrobromide). A-77636 was administered to one group of

primed monkeys (N = 4) previously treated with levodopa and other dopamine receptor agonists, while **SKF 82958** was given to another group of drug-naive monkeys (N = 3). These drugs have different durations of efficacy, lasting >20 h and approx. 1 h, resp., and were administered once daily (A-77636) or thrice daily (**SKF 82958**) for 7 days. Both drugs demonstrated excellent **antiparkinsonian** efficacy and locomotor stimulation. However, a rapid, functionally important, homologous (selective for D1 receptor agonists) desensitization process took place as early as on the second day with the longer -acting drug and a dose escalation of A-77636 failed to restore the initial benefit. Thrice daily dosing at a 4-h interval with the short -acting agent **SKF 82958** maintained the maximal **antiparkinsonian** response but some shortening in the duration of response was obsd. after several days. These behavioral results show that dopamine D1 receptors are susceptible to desensitization after prolonged occupancy and can be desensitized profoundly and independently of dopamine D2 receptors in vivo in this model. Potent dopamine D1 receptor agonists with an intermediate half-life may prove to be better adjuncts in the treatment of **Parkinson**'s disease. Clin. entities with pathol. enhanced dopamine D1 receptor-linked neural transmission might eventually also benefit from such desensitization.

IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(dopamine D1 receptor agonists with intermediate half-life in treatment of **Parkinson**'s disease)

IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(dopamine D1 receptor agonists with intermediate half-life in treatment of **Parkinson**'s disease)

RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



L87 ANSWER 40 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1996:347319 HCAPLUS
DN 125:49040
TI Dyskinesias and tolerance induced by chronic treatment with a D1 agonist administered in pulsatile or continuous mode do not correlate with changes of putaminal D1 receptors in drug-naive MPTP monkeys
AU Goulet, M.; Grondin, R.; Blanchet, P. J.; Bedard, P. J.; Di Paolo, T.
CS School of Pharmacy, Laval University and Department of Molecular Endocrinology, Laval University Medical Centre, Ste-Foy, QC, G1V 4G2, Can.
SO Brain Research (**1996**), 719(1,2), 129-137
CODEN: BRREAP; ISSN: 0006-8993
PB Elsevier
DT Journal
LA English

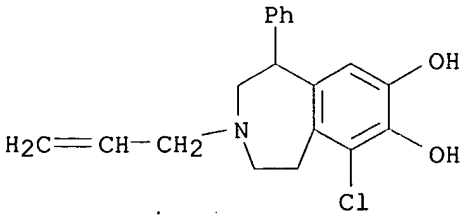
AB Nine monkeys (Macaca fascicularis) were rendered **parkinsonian** after i.v. administration of the toxin MPTP. Three of these animals received pulsatile administration of the D1 receptor agonist **SKF 82958** (1 mg/kg, three times daily) while three were treated by continuous infusion via an osmotic mini-pump with **SKF 82958** (at an equiv. amt. daily) for 29 days. Untreated MPTP as well as healthy control animals were also studied. Relief of **parkinsonian** symptoms was obsd. in the three animals of the pulsatile group. However, dyskinesia occurred in two monkeys which had striatal dopamine depletion of >99 compared to the non-dyskinetic animal slightly less denervated (94). Monkeys receiving continuous **SKF 82958** showed no anti-**parkinsonian** effect and no dyskinesia. All monkeys from the pulsatile and continuous group had measurable amt. of plasma **SKF 82958** as assayed by HPLC with electrochem. detection. In the putamen of all **SKF 82958**-treated monkeys, Bmax of D1 receptors labeled with [3H]SCH 23390 were increased vs. untreated MPTP-monkeys with no change in Kd. In contrast, a decrease D1 receptor d. was obsd. in the nucleus accumbens of untreated MPTP monkeys vs. controls and this was not cor. with either pulsatile or continuous **SKF 82958** treatments. D2 receptor d. measured with [3H]spiperone binding was increased in the posterior putamen of **SKF 82958**-treated monkeys whereas no change was obsd. in the accumbens compared to control animals. Hence, tolerance with the continuous administration of a D1 agonist is not assocd. with a decrease of putaminal D1 or D2 receptor densities and dyskinesia could not be specifically assocd. with an increase of putaminal D1 receptors.

IT **80751-65-1, SKF 82958**
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(dyskinesia and tolerance to continuous administration of D1 agonist assocn. with putaminal D1/D2 receptors)

IT **80751-65-1, SKF 82958**
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(dyskinesia and tolerance to continuous administration of D1 agonist assocn. with putaminal D1/D2 receptors)

RN 80751-65-1 HCAPLUS

CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



L87 ANSWER 41 OF 66 HCAPLUS COPYRIGHT 2003 ACS

AN 1996:304708 HCAPLUS

DN 125:1169

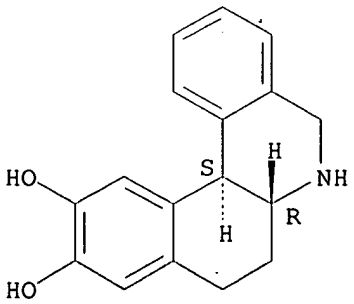
TI The D1 agonist **dihydrexidine** releases acetylcholine and improves cognition in rats

AU Steele, T. D.; Hodges, D. B.; Levesque, T. R.; Locke, K. W.; Sandage, B. W. Jr.

CS Interneuron Pharmaceuticals, Inc., Lexington, MA, 02173, USA

SO Annals of the New York Academy of Sciences (**1996**), 777(Neurobiology of Alzheimers Disease), 427-430
CODEN: ANYAA9; ISSN: 0077-8923
PB New York Academy of Sciences
DT Journal
LA English
AB Neurochem. and behavioral studies have elucidated extensive interactions between dopaminergic and cholinergic systems in brain areas assocd. with movement and cognition. The initial goal of these studies was to evaluate the effect of the anti-**Parkinson** drug **dihydrexidine** (DHX), a dopamine D1 full-efficacy agonist, on brain acetylcholine (ACh) release using in vivo microdialysis techniques. Moderate doses of DHX (3 and 10 mg/kg) produced approx. a 50% increase in striatal ACh release that was blocked by the D1 agonist SCH23390 (0.3 mg/kg). A higher dose of DHX (17.5 mg/kg) was less effective in raising striatal ACh, possibly due to D2 receptor activation. In frontal cortex, DHX (10 mg/kg) evoked a more robust increase in ACh release (+200%) that was blocked by SCH23390 (0.3 mg/kg). Since elevations in brain ACh are assocd. with cognitive improvement, the effectiveness of DHX in a passive avoidance model of learning and memory was also evaluated. These studies revealed a significant improvement in performance by 0.3 mg/kg DHX in scopolamine-induced amnestic rats. These results provided support for the hypothesis that DHX improves cognitive performance as a consequence of ACh release in relevant brain regions. Further, D1 agonists may have novel therapeutic potential in the treatment of dementia.
IT **123039-93-0, Dihydrexidine**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(D1 agonist **dihydrexidine** releases striatal acetylcholine and improves cognition in relation to D1 agonists potential in dementia treatment)
IT **123039-93-0, Dihydrexidine**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(D1 agonist **dihydrexidine** releases striatal acetylcholine and improves cognition in relation to D1 agonists potential in dementia treatment)
RN 123039-93-0 HCAPLUS
CN Benzo[a]phenanthridine-10,11-diol, 5,6,6a,7,8,12b-hexahydro-, (6aR,12bS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L87 ANSWER 42 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1996:155579 HCAPLUS
DN 124:212058
TI Dopamine D1 agonists for the treatment of dementia

IN Locke, Kenneth W.; Steele, Thomas D.
PA Interneuron Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9600062	A1	19960104	WO 1995-US6803	19950530 <--
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KE, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TT, UA, UZ, VN				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5744476	A	19980428	US 1994-266816	19940627 <--
ZA 9504316	A	19960124	ZA 1995-4316	19950526 <--
CA 2193799	AA	19960104	CA 1995-2193799	19950530 <--
AU 9526059	A1	19960119	AU 1995-26059	19950530 <--
EP 767662	A1	19970416	EP 1995-920681	19950530 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
PRAI US 1994-266816		19940627 <--		
WO 1995-US6803		19950530 <--		

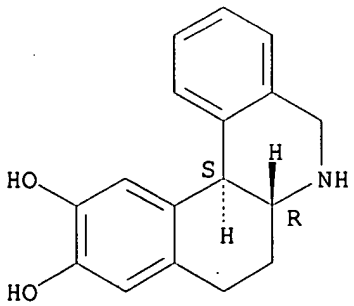
AB A pharmaceutical compn., for treatment of dementia assocd. with neurodegeneration by increasing extracellular brain acetylcholine levels to improve cognition, comprises an effective amt. of a dopamine D1 agonist, e.g. **dihydrexidine**. The compn. further comprises an effective amt. of levodopa, dopamine D agonist, monoamine oxidase inhibitor, acetylcholinesterase inhibitor, apomorphine, muscarinic M1 agonist, or a mixt. thereof.

IT **123039-93-0, Dihydrexidine 174691-84-0**, (+)-**Dihydrexidine**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(dopamine D1 agonists as cognition enhancers for treatment of dementia)

IT **123039-93-0, Dihydrexidine**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(dopamine D1 agonists as cognition enhancers for treatment of dementia)

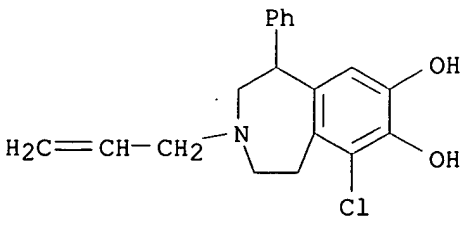
RN 123039-93-0 HCAPLUS
CN Benzo[a]phenanthridine-10,11-diol, 5,6,6a,7,8,12b-hexahydro-, (6aR,12bS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L87 ANSWER 43 OF 66 HCAPLUS COPYRIGHT 2003 ACS

AN 1996:57802 HCAPLUS
DN 124:165044
TI Effect of coadministration of glutamate receptor antagonists and dopaminergic agonists on locomotion in monoamine-depleted rats
AU Gossel, M.; Schmidt, W. J.; Loescher, W.; Zajaczkowski, W.; Danysz, W.
CS Dep. Pharmacol., Merz and Co., Frankfurt/Main, Germany
SO Journal of Neural Transmission: Parkinson's Disease and Dementia Section (**1995**), 10(1), 27-39
CODEN: JNPSEJ; ISSN: 0936-3076
PB Springer
DT Journal
LA English
AB Combinations of dopaminergic agonists with glutamate receptor antagonists have been suggested to be a possible alternative treatment of **Parkinson**'s disease. To gain further insights into this possibility, the antagonist of the competitive AMPA-type glutamate receptor NBQX and the ion-channel blocker of the NMDA glutamate receptor (+)-MK-801 in combination with the dopamine D1 receptor agonists: SKF 38393, **SKF 82958** and **dihydrexidine**; the dopamine D2 receptor agonist bromocriptine and the dopamine-precursor L-DOPA were tested in rats pretreated and with reserpine and .alpha.-methyl-p-tyrosine. MK-801 on its own induced locomotor behavior and potentiated the antiakinetic effects of **dihydrexidine** and L-DOPA but not of the other dopamine agonists tested. NBQX neither on its own nor coadministered with the dopamine agonists tested had an antiakinetic effect. These results indicate that agents, blocking the ion-channel of the NMDA receptor, might be useful adjuvants to some but not all dopaminomimetics in therapy of **Parkinson**'s disease. The same does not seem to be true for the AMPA-antagonist NBQX.
IT **80751-65-1, SKF 82958 123039-93-0, Dihydrexidine**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(effect of coadministration of glutamate receptor antagonists and dopaminergic agonists on locomotion in monoamine-depleted rats)
IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(effect of coadministration of glutamate receptor antagonists and dopaminergic agonists on locomotion in monoamine-depleted rats)
RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



L87 ANSWER 44 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1996:41923 HCAPLUS
DN 124:164950
TI ABT-431: the diacetyl prodrug of **A-86929**, a potent and selective dopamine D1 receptor agonist: in vitro characterization and

effects in animal models of **Parkinson**'s disease

AU Shiosaki, Kazumi; Jenner, Peter; Asin, Karen E.; Britton, Donald R.; Lin, Chun Wei; Michaelides, Michael; Smith, Lance; Bianchi, Bruce; Didomenico, Stanley; et al.

CS Neuroscience Discovery, Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, IL, USA

SO Journal of Pharmacology and Experimental Therapeutics (**1996**), 276(1), 150-60
CODEN: JPETAB; ISSN: 0022-3565

PB Williams & Wilkins

DT Journal

LA English

AB (-)-Trans 9,10-hydroxy-2-propyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[c]phenanthrene hydrochloride (**A-86929**) is a potent and selective full agonist at the dopamine (DA)1 D1-like receptor. Judging by its binding affinities to the D1 and D2 classes of receptors, the compd. is approx. 20-fold D1 receptor-selective, whereas relative potencies based on function in vitro assays indicate that **A-86929** is greater than 400-fold D1-selective. **A-86929** has moderate to weak (Ki > 1 .mu.M) affinity at other monoaminergic and peptidergic receptors, at ion channels and at monoamine uptake sites. The catechol of **A-86929** was bis-acetylated to produce the prodrug, (-)-trans 9,10-acetoxy-2-propyl-4,5,5a,6,7,11-b-hexahydro-3-thia-5-azacyclopent-1-ena[c]phenanthrene hydrochloride (ABT-431), which is more chem. stable yet is rapidly converted to the parent compd. with a half-life of less than 1 min in plasma. Both **A-86929** and ABT-431 produced contralateral rotation in rats bearing unilateral 6-hydroxydopamine lesions, with ED50 values of 0.24 .mu.mol/kg s.c. and 0.54 .mu.mol/kg s.c., resp. **A-86929** and ABT-431 improved behavioral disability scores and increased locomotor activity in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned marmoset model of **Parkinson**'s disease in a dose-dependent manner (the min. ED was 0.10 .mu.mol/kg s.c.). When administered three times daily for 30 consecutive days to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned marmosets, **A-86929** significantly improved disability scores throughout the duration of the study. Current **Parkinson** 's disease therapy includes L-dopa, which stimulates both classes of DA receptors by virtue of its conversion to DA in vivo, and direct-acting D2-selective agonists. Stimulation of the D2 receptor, which is assocd. with all current DA agonist-based therapies, may contribute to their dose-limiting side effects. An agent such as **A-86929** (or its prodrug ABT-431), which selectively stimulates the D1 receptor, may represent a novel mechanism for **Parkinson**'s disease therapy with the potential for an improved side-effect profile and, consequently, improved patient compliance.

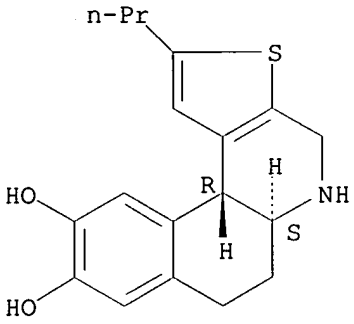
IT **173934-91-3, A 86929**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); **THU (Therapeutic use)**; BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process); USES (Uses)
(ABT-431: the diacetyl prodrug of **A-86929**, a potent and selective dopamine D1 receptor agonist: in vitro characterization and effects in animal models of **Parkinson**'s disease)

IT **166591-11-3**, ABT 431
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(ABT-431: the diacetyl prodrug of **A-86929**, a potent and selective dopamine D1 receptor agonist: in vitro characterization and effects in animal models of **Parkinson**'s disease)

IT **173934-91-3, A 86929**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological

process); BSU (Biological study, unclassified); MFM (Metabolic formation); **THU (Therapeutic use)**; BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process); USES (Uses)
(ABT-431: the diacetyl prodrug of **A-86929**, a potent and selective dopamine D1 receptor agonist: in vitro characterization and effects in animal models of **Parkinson**'s disease)
RN 173934-91-3 HCAPLUS
CN Benzo[f]thieno[2,3-c]quinoline-9,10-diol, 4,5,5a,6,7,11b-hexahydro-2-propyl-, hydrochloride, (5aR,11bS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

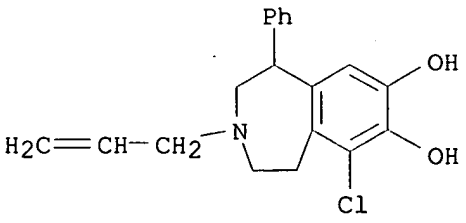


● HCl

L87 ANSWER 45 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1995:924391 HCAPLUS
TI Synthesis and evaluation of novel 8-benzyl-2-aminotetralins as dopamine receptor (D1 and D2) probes
AU Ghosh, Debasis; **Nichols, David E.**; Mayleben, Mechelle; **Mailman, Richard B.**
CS Department Medical Chemistry and Pharmacognosy, Purdue University, West Lafayette, IN, 47907, USA
SO Book of Abstracts, 210th ACS National Meeting, Chicago, IL, August 20-24 (**1995**), Issue Pt. 2, MEDI-128 Publisher: American Chemical Society, Washington, D. C.
CODEN: 61XGAC
DT Conference; Meeting Abstract
LA English
AB For the past several years, we have been examg. .beta.-phenyldopamine as the structural motif of dopamine receptor probes. Previous effort in this direction yielded the first high affinity full dopamine D1 agonist, **dihydrexidine** (1; J. Med Chem., 1990, 33, 1756), that has dramatic efficacy in the MPTP model of **Parkinson**'s disease, and is presently entering clin. trials. To extend our understanding of how the orientation of the pendant Ph ring, relative to the catechol, affects activity, we prepd. 8-benzyl-2-aminotetralins (2a-d; R1, R2 = Me, n-Pr, H) as novel non-rigid analogs of 1. The synthetic strategy and affinity of the products at dopamine D1 and D2 receptors will be presented.

L87 ANSWER 46 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1995:855188 HCAPLUS
DN 123:247462
TI Spare receptors and intrinsic activity: Studies with D1 dopamine receptor agonists
AU Watts, Val J.; Lawler, Cindy P.; Gonzales, Andrea J.; Zhou, Qun-Yong; Civelli, Oliver; **Nichols, David E.**; **Mailman, Richard B.**

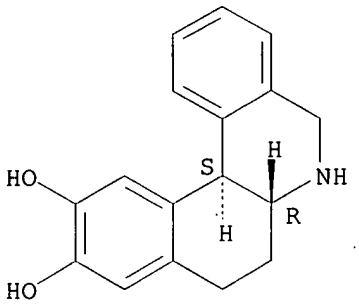
CS Dep. Pharmacology, Psychiatry, Univ. North Carolina Sch. Med., Chapel Hill, NC, 27599-7250, USA
SO Synapse (New York) (**1995**), 21(2), 177-87
CODEN: SYNAET; ISSN: 0887-4476
PB Wiley-Liss
DT Journal
LA English
AB The intrinsic activities of selected dopamine D1 receptor agonists were compared in three distinct mol. expression systems, C-6, Ltk, and GH4 cells transfected with primate D1A receptors. The influence of the cell expression system on intrinsic activity varied markedly among agonists. **Dihydrexidine** (DHX), a potent full agonist with dramatic **antiparkinsonian** actions, displayed intrinsic activity similar to dopamine in all three cell lines. In contrast, **SKF82958** and SKF38393 (full and partial agonists, resp., in rat striatum) had intrinsic activities equal to dopamine in GH4 cells that expressed a high d. of D1 receptors, yet were of lower intrinsic activity in C-6 cells having 15-fold fewer receptors. The idea that spare receptors are one important determinant of obsd. intrinsic activity was explored directly by "receptor titrn.," in which ca. 90% of D1 receptors in Ltk cells were inactivated using EEDQ, an irreversible antagonist. Whereas EEDQ pretreatment decreased potency of all agonists, it changed the intrinsic activity of some, but not all, drugs. A 40% decrease was seen with the partial agonist SKF38393, and, surprisingly, a 30% decrease was seen with the purported full agonist **SKF82958**. Conversely, the intrinsic activity of DHX and A68930 were unaffected by the EEDQ treatment. The data demonstrate that significant and biol. meaningful differences in intrinsic efficacy (e.g., DHX vs. **SKF82958**) may be obscured in test systems that have sufficient receptor reserve (e.g., the striatum). Such differences in intrinsic efficacy may be an important predictor of the clin. utility of D1 agonists.
IT **80751-65-1, SKF 82958 123039-93-0, Dihydrexidine**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(spare receptors and intrinsic activity studied with D1 dopamine receptor agonists)
IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(spare receptors and intrinsic activity studied with D1 dopamine receptor agonists)
RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



L87 ANSWER 47 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1995:775038 HCAPLUS
DN 123:188251
TI Determinants of dopamine D1 receptor agonist activity (**Parkinson's disease, dihydrexidine**)

AU Watts, Val J.
CS Univ. of North Carolina, Chapel Hill, NC, USA
SO (**1994**) 129 pp. Avail.: Univ. Microfilms Int., Order No. DA9523106
From: Diss. Abstr. Int., B 1995, 56(2), 759
DT Dissertation
LA English
AB Unavailable
IT **123039-93-0, Dihydrexidine**
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(determinants of dopamine D1 receptor agonist **dihydrexidine** activity in therapy for **parkinsonism**)
IT **123039-93-0, Dihydrexidine**
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(determinants of dopamine D1 receptor agonist **dihydrexidine** activity in therapy for **parkinsonism**)
RN 123039-93-0 HCAPLUS
CN Benzo[a]phenanthridine-10,11-diol, 5,6,6a,7,8,12b-hexahydro-, (6aR,12bS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



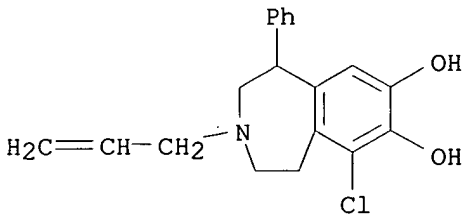
L87 ANSWER 48 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1995:659182 HCAPLUS
DN 123:74740
TI "Full" dopamine D1 agonists in human caudate: biochemical properties and therapeutic implications
AU Gilmore, J. H.; Watts, V. J.; Lawler, C. P.; Noll, E. P.; **Nichols, D. E.**; **Mailman, R. B.**
CS Dep. Psychiatry, Pharmacology & Medicinal Chemistry, Brain & Dev Res Ctr, Univ. of North Carolina School of Medicine, Chapel Hill, NC, 27599-7160, USA
SO Neuropharmacology (**1995**), 34(5), 481-8
CODEN: NEPHBW; ISSN: 0028-3908
PB Elsevier
DT Journal
LA English
AB Recent data indicate that full D1 dopamine agonists have greater **antiparkinsonian** effects in the MPTP primate model than do partial agonists, suggesting that the intrinsic activity of D1 agonists may affect their utility in the treatment of **Parkinson**'s disease. It is unclear, however, whether human D1 receptors in situ are similar to D1 receptors in other species or in mol. expression systems. For this reason, the binding affinity and functional activity of a series of D1 dopamine receptor agonists[**dihydrexidine** (DHX), **SKF82958**, and A68930] were detd. in postmortem human caudate. Results from in vitro binding studies with membranes from human caudate indicate that these D1 agonists competed for [3H]SCH23390 labeled sites with a rank order similar to that found in rat striatum [K50 = 36.8 nM (DHX); 18.6 nM

(**SKF82958**); 3.9 nM (A68930)]. The ability of these compds. and the partial agonist SKF38393 to stimulate the enzyme adenylyl cyclase in tissue homogenates of human caudate was also examd. DHX and A68930 are full agonists compared to dopamine, whereas **SKF82958** and SKF38393 are partial agonists. These differences in biochem. intrinsic activity are consistent with the profound **antiparkinsonian** effects caused by DHX, but not by **SKF82958** and SKF383893, in the MPTP-monkey model. This suggests that DHX and A68930 may be of greater utility in treating disorders where a full efficacy D1 agonist may be required.

IT **80751-65-1, SKF82958 123039-93-0, Dihydrexidine**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(full dopamine D1 agonists in human caudate: biochem. properties and therapeutic implications)

IT **80751-65-1, SKF82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(full dopamine D1 agonists in human caudate: biochem. properties and therapeutic implications)

RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



L87 ANSWER 49 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1995:654435 HCAPLUS
DN 123:53514
TI **Dihydrexidine**, a full D1 dopamine receptor agonist, induces rotational asymmetry in **hemiparkinsonian** monkeys
AU Johnson, B. J.; Peacock, V.; Schneider, J. S.
CS Dep. Neurol., Hahnemann Univ., Philadelphia, PA, 19102, USA
SO Pharmacology, Biochemistry and Behavior (**1995**), 51(4), 617-22
CODEN: PBBHAU; ISSN: 0091-3057
PB Elsevier
DT Journal
LA English
AB **Dihydrexidine** (trans-10,11-dihydroxy-5,6,6a,7,8,12b-hexanhydrobenzo[a]phenanthridine) is a full dopamine D1 agonist. In rhesus macaque monkeys rendered **hemiparkinsonian** by unilateral intracarotid infusions of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), **dihydrexidine** (0.15-0.9 mg/kg) elicited dose-dependent contralateral rotation. The effects of **dihydrexidine** were blocked by pretreatment with the D1 antagonist SCH 23390 (0.03 mg/kg), but not by the D2 antagonist raclopride (0.025 mg/kg). These results suggest a functional role for D1 receptors in stimulating motor behavior in a primate model of **Parkinson**'s disease.

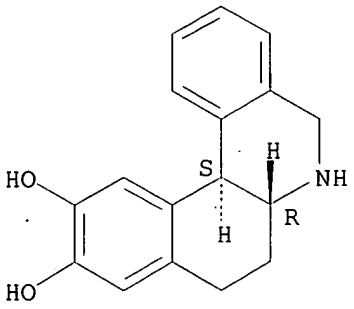
IT **123039-93-0, Dihydrexidine**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); BIOL (Biological study)
(**dihydrexidine** induction of rotational asymmetry in **hemiparkinsonian** monkeys in relation to D1 receptor role in stimulating motor behavior in **Parkinson**'s disease primate model)

IT **123039-93-0, Dihydrexidine**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**dihydrexidine** induction of rotational asymmetry in **hemiparkinsonian** monkeys in relation to D1 receptor role in stimulating motor behavior in **Parkinson**'s disease primate model)

RN 123039-93-0 HCAPLUS
CN Benzo[a]phenanthridine-10,11-diol, 5,6,6a,7,8,12b-hexahydro-, (6aR,12bS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



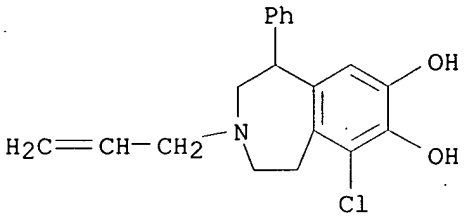
L87 ANSWER 50 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1995:505682 HCAPLUS
DN 122:256247
TI Combination treatment of the partial D2 agonist terguride with the D1 agonist **SKF 82958** in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned **Parkinsonian** cynomolgus monkeys
AU Akai, Tetsuo; Ozawa, Masaki; Yamaguchi, Motonori; Mizuta, Eiji; Kuno, Sadako
CS Research Dep., Inst. Pharma Research, Development and Medical Science, Osaka, Japan
SO Journal of Pharmacology and Experimental Therapeutics (**1995**), 273(1), 309-14
CODEN: JPETAB; ISSN: 0022-3565
PB Williams & Wilkins
DT Journal
LA English
AB The optimal combination of a dopamine D2 agonist and a D1 agonist was evaluated for symptomatic treatment of **Parkinson**'s disease. Behavioral effects of combination treatment of the full D2 agonist quinpirole or the partial D2 agonist terguride with the full D1 agonist **SKF 82958** [(I) 6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2, 3, 4, 5-tetra-hydro-1H-3-benzazepine] were investigated in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned and **parkinsonian** cynomolgus monkeys with attention to the induction of hyperactivity such as irritability, excitability and aggressiveness and of dyskinesias such as licking of paws, chewing and biting. Both quinpirole and **SKF 82958** alone improved the **parkinsonism** with a slight induction of the hyperactivity and dyskinesias. Terguride also improved the **parkinsonism** but did not induce the hyperactivity and dyskinesias. Combination treatment of quinpirole with **SKF 82958** not only showed a tendency to augment the

antiparkinsonian effects but also induced the marked hyperactivity and dyskinesias. On the other hand, combination treatment of terguride with **SKF 82958** also augmented the **antiparkinsonian** effects but did not induce any hyperactivity and dyskinesias. These findings suggest that combination therapy with a partial D2 agonist and a full D1 agonist or monotherapy with a dopamine agonist that has both partial D2 and full D1 agonist properties might be beneficial for treating motor dysfunction in **Parkinson**'s disease without inducing dopaminergic side effects.

IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(**antiparkinsonian** effect of combination treatment of D2 agonist terguride or quinpirole with D1 agonist **SKF 82958**)

IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(**antiparkinsonian** effect of combination treatment of D2 agonist terguride or quinpirole with D1 agonist **SKF 82958**)

RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



L87 ANSWER 51 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1995:412216 HCAPLUS
DN 122:178283
TI The differential behavioral effects of benzazepine D1 dopamine agonists with varying efficacies, co-administered with quinpirole in primate and rodent models of **Parkinson**'s disease
AU Gnanalingham, Kanna K.; Hunter, A. Jackie; Jenner, Peter; Marsden, C. David
CS Parkinson's Dis. Soc. Experimental Res. Lab., Biomed. Sci. Div., King's College, London, UK
SO Psychopharmacology (Berlin) (**1995**), 117(3), 287-97
CODEN: PSCHDL; ISSN: 0033-3158
PB Springer
DT Journal
LA English
AB The effects of co-administration of quinpirole with benzazepine D1 dopaminergic agonists possessing full/supramaximal (SKF 80723 and **SKF 82958**), partial (SKF 38393 and SKF 75670) and no efficacies (SKF 83959) in stimulating adenylate cyclase (AC) were investigated in rodent and primate models of **Parkinson**'s disease (PD). In rats with a unilateral 6-hydroxydopamine (6-OHDA)-induced lesion of the medial forebrain bundle, co-administration of SKF 38393 (7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine), SKF 75670 (its 3-Me analog), SKF 80723 (6-Br analog), SKF 83959 (6-Cl, 3-Me, 3'-Me

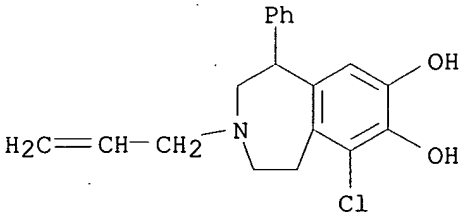
analog) and **SKF 82958** (6-Cl, 3-Pr analog) strongly potentiated the contralateral circling induced by quinpirole. In MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-treated common marmosets, administration of quinpirole alone increased locomotor activity and reversed motor deficits. Grooming and oral activities were unaltered. Co-administration of SKF 38393 and SKF 75670 inhibited the quinpirole-induced changes in locomotor activity and motor disability. The combined treatment with SKF 80723 or **SKF 82958** plus quinpirole had no overall effect on locomotor activity or motor disability. In contrast, SKF 83959 extended the duration of the quinpirole-induced increase in locomotor activity, with corresponding decreases in motor disability. Co-administration of high doses of **SKF 82958**, and more esp. SKF 83959 and SKF 80723, with quinpirole induced hyperexcitability and seizures. Oral activity and grooming were unaltered following the co-administration of the benzazepine derivs. with quinpirole. The ability of some benzazepine-type dopaminergic D1 agonists to prolong the **antiparkinsonian** effects of quinpirole in the MPTP-treated marmoset may indicate a role for certain D1 agonists in the clin. treatment of PD. In general, the behavioral responses to the combined administration of benzazepines with quinpirole in the 6-OHDA-lesioned rat and more esp. the MPTP-treated marmoset failed to correlate with their ability to stimulate AC. These observations further implicate a behavioral role for dopaminergic D1 receptors not linked to AC.

IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(dopamine agonists of benzazepine type plus quinpirole effect on models of **Parkinson**'s disease)

IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(dopamine agonists of benzazepine type plus quinpirole effect on models of **Parkinson**'s disease)

RN 80751-65-1 HCAPLUS

CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



L87 ANSWER 52 OF 66 HCAPLUS COPYRIGHT 2003 ACS

AN 1995:412215 HCAPLUS

DN 122:178282

TI Differential anti-**Parkinsonian** effects of benzazepine D1 dopamine agonists with varying efficacies in the MPTP-treated common marmoset

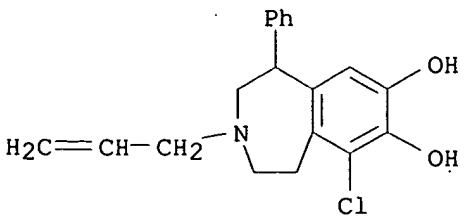
AU Gnanalingham, Kanna K.; Erol, Dilek D.; Hunter, A. Jackie; Smith, Lance A.; Jenner, Peter; Marsden, C. David

CS Parkinson's Disease Society Experimental Res. Lab., Biomedical Sci. Div., King's Coll., London, UK

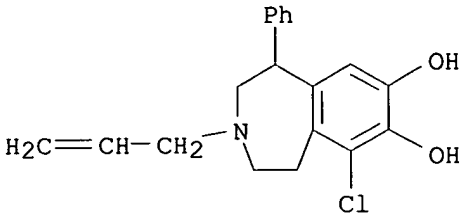
SO Psychopharmacology (Berlin) (**1995**), 117(3), 275-86
CODEN: PSCHDL; ISSN: 0033-3158

PB Springer

DT Journal
LA English
AB In common marmosets systemically treated with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), the behavioral effects of benzazepine D1 dopamine (DA) agonists with full/supramaximal (SKF 80723 and **SKF 82958**), partial (SKF 38393, SKF 75670 and SKF 83565) and no efficacies (SKF 83959) in stimulating adenylate cyclase (AC) activity were investigated. The benzazepine derivs., with the exception of **SKF 82958** (8-fold D1 DA receptor selectivity), demonstrated high D1 DA receptor affinity and selectivity (approx. 100-fold or more) in rat striatal homogenates. Administration of MPTP in marmosets induced locomotor hypoactivity, rigidity and motor disability. SKF 38393 (7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine) and SKF 75670 (3-CH3 analog) further reduced locomotor activity (by -70 to -80%) and increased motor disability (by +22 to +67%) in these animals. SKF 83565 (6-Cl, 3-CH3, 3'-Cl analog) and **SKF 82958** (6-Cl, 3-C3H5 analog) had only a slight effect on locomotor activity but decreased motor disability at high doses (-46 to -60%). In contrast, SKF 83959 (6-Cl, 3-CH3, 3'-CH3 analog) and SKF 80723 (6-Br analog) produced pronounced increases in locomotion (6-10 fold) and a reversal in motor disability (by -64 to -77%). Oral activity, consisting largely of abnormal, 'dyskinetic' tongue protrusions and vacuous chews, was increased in animals treated with SKF 38393, SKF 83565, **SKF 82958** and more esp. with SKF 80723 and SKF 83959. Grooming was increased with **SKF 82958** and more esp. with SKF 80723 and SKF 83959. In contrast, quinpirole (D2 DA agonist), reversed the MPTP-induced motor deficits in the marmoset, with no effect on grooming and oral activity. The present findings further demonstrate the **antiparkinsonian** actions of some D1 DA agonists in MPTP-treated primates. However, in general the behavioral effects of benzazepines failed to correlate with either their D1 DA receptor affinity/selectivity or their efficacy in stimulating adenylate cyclase (AC) activity. These observations further implicate a behavioral role for D1 DA receptors uncoupled to AC and/or a role for extrastriatal D1 DA receptors in mediating the behavioral response to D1 DA agonists.
IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(differential anti-**Parkinsonian** effects of benzazepine D1 dopamine agonists with varying efficacies in the MPTP-treated common marmoset)
IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(differential anti-**Parkinsonian** effects of benzazepine D1 dopamine agonists with varying efficacies in the MPTP-treated common marmoset)
RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)

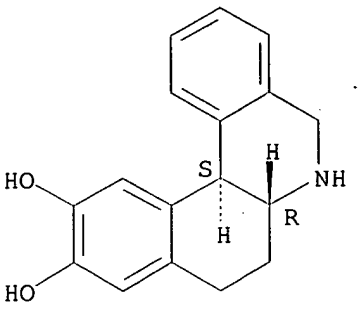


L87 ANSWER 53 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1995:405472 HCAPLUS
DN 122:204995
TI Behavioral involvement of central dopamine D1 and D2 receptors in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned **Parkinsonian** cynomolgus monkeys
AU Akai, Tetsuo; Ozawa, Masaki; Yamaguchi, Motonori; Mizuta, Eiji; Kuno, Sadako
CS Inst. Pharma Res., Dev. Med. Sci., Nihon Schering K.K., Osaka, 532, Japan
SO Japanese Journal of Pharmacology (**1995**), 67(2), 117-24
CODEN: JJPAAZ; ISSN: 0021-5198
PB Japanese Pharmacological Society
DT Journal
LA English
AB To clarify the roles of dopamine D1 and D2 receptors in behavioral symptoms of **Parkinson**'s disease, **antiparkinsonian** effects of various dopamine agonists in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned **Parkinsonian** monkeys were investigated with regard to induction of hyperactivity such as excitability, irritability and aggressiveness. The non-selective dopamine agonist apomorphine ameliorated the **Parkinsonism**, but induced marked hyperactivity dose-dependently. Pretreatment with either the dopamine D1 antagonist SCH23390 or the dopamine D2 antagonist sulpiride markedly suppressed the apomorphine-induced hyperactivity with slight attenuation of the **antiparkinsonian** effects. Both the dopamine D2-receptor agonist quinpirole and the dopamine D1-receptor agonist **SKF 82958** ameliorated the **parkinsonism** in a dose-dependent manner with a slight induction of hyperactivity. Combination treatment of a threshold dose of quinpirole with that of **SKF 82958** augmented the **antiparkinsonian** effects without a marked induction of hyperactivity. However, the combination treatment at higher doses induced marked hyperactivity accompanied by augmented **antiparkinsonian** effects. These results suggest that stimulation of either central dopamine D1 or D2 receptors is requisite for the **antiparkinsonian** effects and concurrent strong stimulation of both central dopamine D1 and D2 receptors causes marked hyperactivity which may be predictive of dopaminergic psychiatric side effects.
IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(dopamine D1 and D2 receptor stimulation dependence in **antiparkinsonian** drug effects in relation to hyperactivity)
IT **80751-65-1, SKF 82958**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(dopamine D1 and D2 receptor stimulation dependence in **antiparkinsonian** drug effects in relation to hyperactivity)
RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



L87 ANSWER 54 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1995:217434 HCAPLUS
DN 122:927
TI Effects of **dihydrexidine**, a full dopamine D-1 receptor agonist, on delayed response performance in chronic low dose MPTP-treated monkeys
AU Schneider, J. S.; Sun, Z.-Q.; Roeltgen, D. P.
CS Center for Neurological Research of the Department of Neurology, Hahnemann University, Broad and Vine Streets, Mail Stop 423, Philadelphia, PA, 19102, USA
SO Brain Research (**1994**), 663(1), 140-4
CODEN: BRREAP; ISSN: 0006-8993
PB Elsevier
DT Journal
LA English
AB Monkeys exposed to low doses of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) over long periods of time develop cognitive deficits without severe **Parkinsonian** motor signs. In the present study the authors assessed the effects of the selective and full dopamine D-1 receptor agonist **dihydrexidine** on delayed response deficits in chronic low dose (CLD) MPTP-treated monkeys. **Dihydrexidine** caused a dose-dependent improvement in task performance, that could be blocked by the D-1 receptor antagonist SCH-23390. In addn. to reducing the no. of mistakes made during delayed response performance, **dihydrexidine** also improved task persistence. These data suggest that **dihydrexidine** may be useful in treating cognitive as well as motor deficits of **parkinsonism**.
IT **123039-93-0, Dihydrexidine**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(delayed response performance response to dopamine D1 agonist **dihydrexidine** in MPTP-treated monkey model of **parkinsonism**)
IT **123039-93-0, Dihydrexidine**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(delayed response performance response to dopamine D1 agonist **dihydrexidine** in MPTP-treated monkey model of **parkinsonism**)
RN 123039-93-0 HCAPLUS
CN Benzo[a]phenanthridine-10,11-diol, 5,6,6a,7,8,12b-hexahydro-, (6aR,12bS)-rel- (9CI) (CA INDEX NAME)

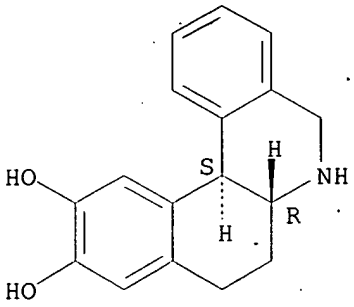
Relative stereochemistry.



L87 ANSWER 55 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1994:645104 HCAPLUS
DN 121:245104
TI Dopaminergic Benzo[a]phenanthridines: Resolution and Pharmacological Evaluation of the Enantiomers of **Dihydrexidine**, the Full Efficacy D1 Dopamine Receptor Agonist
AU Knoerzer, Timm A.; **Nichols, David E.**; Brewster, William K.; Watts, Val J.; Mottola, David; **Mailman, Richard B.**
CS School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN, 47907, USA
SO Journal of Medicinal Chemistry (**1994**), 37(15), 2453-60
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
AB Racemic trans-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[a]phenanthridine (2, **dihydrexidine**) was shown previously to be the first bioavailable full efficacy agonist at the D1 dopamine receptor. In addn. to its full D1 agonist properties, 2 also is a good ligand for D2-like dopamine receptors. The profound anti-**Parkinsonian** actions of this compd. make detn. of its enantioselectivity at both D1 and D2 receptors of particular importance. To accomplish this, the enantiomers were resolved by prepn. of diastereomeric (R)-O-methylmandelic acid amides of racemic trans-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[a]phenanthridine 4 that were then sepd. by centrifugal chromatog. An X-ray anal. of the (-)-N-(R)-O-methylmandel diastereoamide revealed the abs. configuration to be 6aS,12bR. Removal of the chiral auxiliary and O,O-deprotection afforded enantiomeric amines that were then tested for biol. activity. In striatal membranes, the (6aR,12bS)-(+)-enantiomer 2 had about twice the affinity of the racemate and 25-fold greater affinity than the (-)-enantiomer at the D1 receptor labeled by [3H]SCH23390 (K0.5s of 5.6, 11.6, and 149 nM, resp.). Similarly, the (+)-enantiomer 2 had about twice the affinity of the racemate for human D1 receptors expressed in transfected Ltk- cells. Functionally, the (+)-enantiomer of 2 was a full agonist, with an EC50 of 51 nM in activating striatal dopamine-sensitive adenylate cyclase vs. 2.15 .mu.M for the (-)-enantiomer. With respect to D2-like receptors, (+)-2 had a K0.5 of 87.7 nM in competing with [3H]spiperone at D2 binding sites in rat striatal membranes vs. about 1 .mu.M for the (-)-enantiomer. Together, these data demonstrate that both the D1 and D2 activities of **dihydrexidine** reside principally in the (6aR,12bS)-(+)-enantiomer. The results are discussed in the context of structure-activity relationships and conceptual models of the D1 receptor.
IT **158704-02-0**
RL: BIOL (Biological study)
(resoln. and dopamine-agonist activity of, structure in relation to)
IT **158704-02-0**
RL: BIOL (Biological study)
(resoln. and dopamine-agonist activity of, structure in relation to)

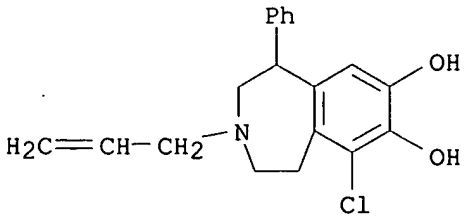
RN 158704-02-0 HCAPLUS
CN Benzo[a]phenanthridine-10,11-diol, 5,6,6a,7,8,12b-hexahydro-, hydrochloride, (6aR,12bS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

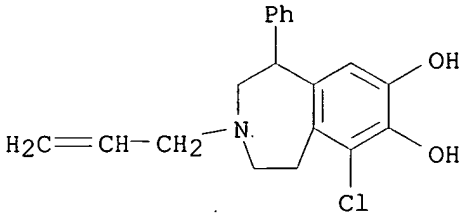


● HCl

L87 ANSWER 56 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1994:95433 HCAPLUS
DN 120:95433
TI Relative potency and efficacy of some dopamine agonists with varying selectivities for D1 and D2 receptors in MPTP-induced **hemiparkinsonian** monkeys. [Erratum to document cited in CA119(11):108900h]
AU Domino, Edward F.; Sheng, Jiangjun
CS Dep. Pharmacol., Univ. Michigan, Ann Arbor, MI, USA
SO Journal of Pharmacology and Experimental Therapeutics (**1993**), 267(1), 566
CODEN: JPETAB; ISSN: 0022-3565
DT Journal
LA English
AB The errors were not reflected in the abstr. or the index entries.
IT **80751-65-1**
RL: BIOL (Biological study)
(circling behavior in **parkinsonism** model response to (Erratum))
IT **80751-65-1**
RL: BIOL (Biological study)
(circling behavior in **parkinsonism** model response to (Erratum))
RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



L87 ANSWER 57 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1994:45681 HCAPLUS
DN 120:45681
TI Effects of D-1 DA receptor agonists on **Parkinsonism** induced by MPTP in the common marmoset
AU Nomoto, Masahiro; Fukuda, Takeao
CS Fac. Med., Kagoshima Univ., Japan
SO Yakubutsu, Seishin, Kodo (**1991**), 11(6), 394
CODEN: YSKODB; ISSN: 0285-5313
DT Journal
LA Japanese
AB D-1 dopamine receptor agonists **SKF82958** and CY208-243 increased the lowered automatic movement and inhibited the akinesia in 1-methyl-4-phenyl-1,2,3,6-tetrahydrophridine (MPTP)-induced **parkinsonism** in common marmoset, whereas SKF38393 had no such effects.
IT **80751-65-1, SKF-82958**
RL: BIOL (Biological study)
(dopamine D1 receptor agonist, akinesia in methylphenyltetrahydropyridine-induced **parkinsonism** response to)
IT **80751-65-1, SKF-82958**
RL: BIOL (Biological study)
(dopamine D1 receptor agonist, akinesia in methylphenyltetrahydropyridine-induced **parkinsonism** response to)
RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



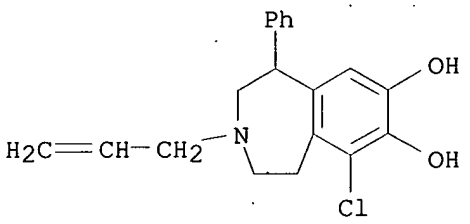
L87 ANSWER 58 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1994:23456 HCAPLUS
DN 120:23456
TI Differential effect of selective D-1 and D-2 dopamine receptor agonists on levodopa-induced dyskinesia in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-exposed monkeys
AU Blanchet, P.; Bedard, P. J.; Britton, D. R.; Kebabian, J. W.
CS Cent. Rech. Neurobiol., Hop. Enfant-Jesus, Quebec, QC, Can.
SO Journal of Pharmacology and Experimental Therapeutics (**1993**), 267(1), 275-9
CODEN: JPETAB; ISSN: 0022-3565
DT Journal
LA English
AB The motor effects of selective D-1 dopamine receptor stimulation in **Parkinson**'s disease have been explored in a limited no. of studies with partial D-1 agonists only and the results were unsatisfactory. Four 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-exposed **parkinsonian** monkeys already exhibiting levodopa- and dopamine agonist-induced dyskinesia received selective D-1 agonists ([2,3,4,5-tetrahydro-7-8-dihydroxy-1-phenyl-1-H-3-benzazepine-HC] (SKF 38393), [(.+-.)6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzapine hydrobromide]

(**SKF 82958**), [(1R,3S)3-(1'-adamantyl)-1-aminomethyl-3,4-dihydro-5,6-dihydroxy-1H-2-benzopyran hydrochloride] (A-77636) and [(-)-(6aR)(12bR)-4,6,61,7,8,12b-hexahydro-7-methylindolo (4,3-ab)-phenanthridine] (CY 208-243)) to compare these drugs with selective D-2 agonists (LY 171555, (+)-4-propyl-9-hydroxynaphthoxazine and bromocriptine) and levodopa in terms of **antiparkinsonian** efficacy and side effects. The D-1 class of compds. was as efficacious as the D-2 agents in alleviating **parkinsonism** in these animals. However, D-1 agonists were, in general, less likely to reproduce dyskinesia. In addn., D-1 agonists occasionally improved motor symptoms without concomitant dyskinesia, unlike D-2 agonists or levodopa (which always produced some dyskinesia with improvement in motor function). These preliminary results do not support the hypothesis that preferential D-1 receptor stimulation facilitates dyskinesia in primates. The authors propose that this strategy could lead to a new equil. in the neural inputs integrated by the medial globus pallidus, thereby explaining the better therapeutic profile seen with the selective D-1 agonists used.

IT **80751-65-1, SKF 82958**
RL: BIOL (Biological study)
(**antiparkinsonian** activity of, dyskinesia redn. in relation to)

IT **80751-65-1, SKF 82958**
RL: BIOL (Biological study)
(**antiparkinsonian** activity of, dyskinesia redn. in relation to)

RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



L87 ANSWER 59 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1994:23378 HCAPLUS
DN 120:23378
TI Dopamine D1 receptors: Efficacy of full (**dihydrexidine**) vs. partial (SKF38393) agonists in primates vs. rodents
AU Watts, Val J.; Lawler, Cindy P.; Gilmore, John H.; Southerland, Stan B.; **Nichols, David E.; Mailman, Richard B.**
CS Sch. Med., Univ. North Carolina, Chapel Hill, NC, 27599-7250, USA
SO European Journal of Pharmacology (**1993**), 242(2), 165-72
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
AB Although partial efficacy dopamine D1 receptor agonists have little therapeutic benefit in **parkinsonism**, the first high potency, full efficacy dopamine D1 receptor agonist **dihydrexidine** recently has been shown to have profound **antiparkinsonian** effects. One reason for the greater **antiparkinsonian** effects of **dihydrexidine** vs. SKF38393 might be that SKF38393, while a partial dopamine D1 receptor agonist in rodent striatal prepns., has virtually no agonist activity in monkey striatum (Pifl et al., 1991). To explore this hypothesis, the authors compared the dopamine D1 receptor affinity and efficacy of **dihydrexidine** and SKF38393 in striatum from rat and

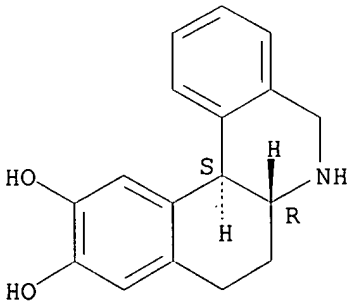
monkey. In vitro binding studies using membranes from putamen of adult rhesus monkeys demonstrated that dihydroexidine competed for dopamine D1 receptors (labeled with [3H]SCH23390) with high potency (IC50 = 20 nM vs. ca. 10 nM in rat brain). SKF38393 was about 4-fold less potent than **dihydrexidine** in both monkey and rat brain. The in vitro functional activity of these drugs was assessed by their ability to stimulated adenylate cyclase activity in tissue homogenates. **Dihydrexidine** was of full efficacy (relative to dopamine) in stimulating cAMP synthesis in both monkey and rat. SKF38393 was only a partial efficacy agonist in both rat striatum and monkey putamen, but contrary to the original hypothesis, it had the same efficacy (ca. 40% relative to dihydrexideine) in membranes from both species. Interestingly, greater between-subject variation was found in the stimulation produced by SKF38393 in primate compared to rat brain, although the basis for this variation is unclear. The present data demonstrate for the first time that **dihydrexidine** is a full efficacy dopamine D1 receptor agonist in primate brain. Moreover, these data indicate that the partial efficacy dopamine D1 receptor agonist SKF38393 causes the same relative response (compared to dopamine) in at and monkey dopamine D1 receptors. Together, this information suggests that the **antiparkinsonian** effect of **dihydrexidine** vs. the relative inactivity of SKF38393 is not due to the fact that primate brains are simply unresponsive to SKF38393.

IT **123039-93-0, Dihydrexidine**
RL: BIOL (Biological study)
(SKF38393 vs. full dopamine D1 receptor agonist, in primates vs. rodents efficacy of, **Parkinsonism** therapy in relation to)

IT **123039-93-0, Dihydrexidine**
RL: BIOL (Biological study)
(SKF38393 vs. full dopamine D1 receptor agonist, in primates vs. rodents efficacy of, **Parkinsonism** therapy in relation to)

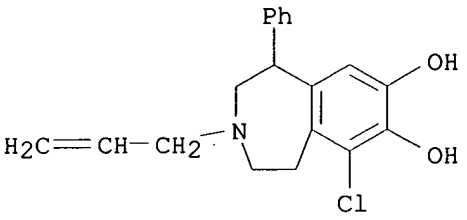
RN 123039-93-0 HCAPLUS
CN Benzo[a]phenanthridine-10,11-diol, 5,6,6a,7,8,12b-hexahydro-, (6aR,12bS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L87 ANSWER 60 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1993:508900 HCAPLUS
DN 119:108900
TI Relative potency and efficacy of some dopamine agonists with varying selectivities for D1 and D2 receptors in MPTP-induced **hemiparkinsonian** monkeys
AU Domino, Edward F.; Sheng, Jiangjun
CS Dep. Pharmacol., Univ. Michigan, Ann Arbor, MI, USA
SO Journal of Pharmacology and Experimental Therapeutics (**1993**), 265(3), 1387-91
CODEN: JPETAB; ISSN: 0022-3565
DT Journal

LA English
AB A series of dopamine agonists were studied on contraversive circling behavior in monkeys with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced **hemiparkinsonism**. The compds. selected were [1R,3S]3-(1'-adamantyl)-1-aminomethyl-3,4-dihydro-5,6-dihydroxy-1H-2-benzopyran-HCl (A-77636), L-dopa-Me ester, (-)-2-[N-propyl-N-(2-thienyl)ethylamino-5-hydroxytetralin]-HCl (N-0923), pergolide, (+)-(4aR)-trans-3,4,4a,5,6,10b-hexahydro-4-propyl-2H-naphth[1,2-b]-1,2-oxazin-9-ol (PHNO), (.+-.)6-chloro-7,8-dihydroxy-2,3,4,5-tetrahydro-1-phenyl-1H-3-benzazepine-HBr (SKF-81297) and (.+-.)6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine-HBr (**SKF-82958**). The dose-effect relationship of each of these compds. was detd. by measuring the no. of contraversive turns in 120 min after an i.m. injection. There were marked differences in the potency and efficacy of the various compds. studied. The most potent compds. were the selective D2 agonists PHNO and N-0923. L-Dopa Me ester was equally effective, but much less potent. The D1 agonist A-77636 was equally effective. The D1 agonist **SKF-82958** was also effective, but less potent.
The D1 agonist SKF-81297 was ineffective. With the exception of L-dopa Me ester, the greater the D1/D2 affinity ratio, the greater the ED50 to induce contraversive circling.
IT **80751-65-1, SKF 82958**
RL: BIOL (Biological study)
(circling behavior in **parkinsonism** model response to)
IT **80751-65-1, SKF 82958**
RL: BIOL (Biological study)
(circling behavior in **parkinsonism** model response to)
RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



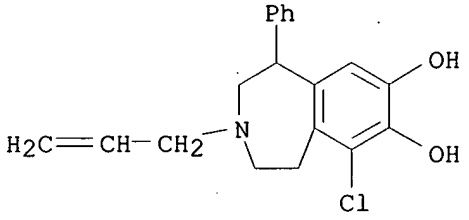
L87 ANSWER 61 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1993:139717 HCAPLUS
DN 118:139717
TI Sensitization, response fluctuation and long-term effect of **SKF-82958** and bromocriptine in the hemi-**parkinsonian** rat
AU Silverman, Peter B.
CS Health Sci. Cent., Univ. Texas, Houston, TX, 77030-3497, USA
SO European Journal of Pharmacology (**1993**), 229(2-3), 235-40
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
AB Rats with a unilateral 6-hydroxydopamine lesion of the brain substantia nigra were treated with the dopamine agonists **SKF-82958** (D1 receptor-selective) or bromocriptine (D2 receptor-selective) and their circling behavior responses were recorded. Both compds. induced an acute episode of rotation directed away from the lesioned side. Consecutive daily treatments with either compd. usually increased the av. response (sensitization) over a 3-6-day treatment period. Nearly all animals treated with low doses of **SKF-82958** or bromocriptine had one or more days when they were totally unresponsive to the drug

treatment. Thus, the response fluctuations were not exclusively assocd. with D1 or D2 receptor agonist treatments. When subsequently tested in the drug-assocd. environment at 2, 4, and 10 wk after the last drug treatment, rats previously treated with **SKF-82958** exhibited rapid contralateral rotation while rats previously treated with bromocriptine showed no such drug-free rotation. This result is consistent with previous findings that the D1 receptor agonist SKF-38393, but not the D2 receptor agonist quinpirole, had long-term behavioral effects in nigral rats, and suggests that persistent motor consequences of limited treatment with dopamine receptor agonists are D1 receptor-related.

IT **80751-65-1, SKF-82958**
RL: BIOL (Biological study)
(**parkinsonism** treatment by, response fluctuation and sensitization in)

IT **80751-65-1, SKF-82958**
RL: BIOL (Biological study)
(**parkinsonism** treatment by, response fluctuation and sensitization in)

RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



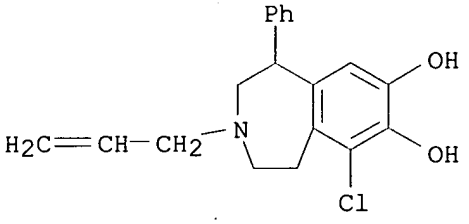
L87 ANSWER 62 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1993:94251 HCAPLUS
DN 118:94251
TI N-Methyl-D-aspartate receptor antagonist and dopamine D1 and D2 agonist interactions in 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine-induced **hemiparkinsonian** monkeys
AU Domino, Edward F.; Sheng, Jiangjun
CS Dep. Pharmacol., Univ. Michigan, Ann Arbor, MI, USA
SO Journal of Pharmacology and Experimental Therapeutics (**1993**), 264(1), 221-5
CODEN: JPETAB; ISSN: 0022-3565
DT Journal
LA English
AB The noncompetitive N-methyl-D-aspartate antagonist (5R,10S)-(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine hydrogen maleate (MK-801) and three dopamine agonists [(.+-.)6-chloro-7,8-dihydroxy-2,3,4,5-tetrahydro-1-phenyl-1H-3-benzazepine hydrobromide (SKF-81297), (.+-.)6,chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide (**SKF-82958**) selective for D1 and (-)-2-[N-propyl-N-(2-thienyl)ethyl-amino-5-hydroxytetralin] hydrochloride (N-0923) selective for D2 receptors] were studied in seven adult female **hemiparkinsonian** Macaca nemestrina monkeys. Video recordings of free circling behavior showed that both **SKF-82958** and N-0923 produced dose-related mean increases in contraversive rotations during the 120-min period after i.m. injection. SKF-81297 (21.1, 67.8 and 210.7 .mu.g/kg) was relatively inactive compared to **SKF-82958** (24.8, 74.8 and 234 .mu.g/kg). The selective D2 agonist N-0923 (3.2, 10 and 32 .mu.g/kg, i.m.) was the most potent in producing contraversive circling behavior. The noncompetitive

N-methyl-D-aspartate antagonist dizocilpine (MK-801), in doses of 10 and 32 .mu.g/kg i.m., produced a very slight increase in contraversive circling in contrast to the selective dopamine agonist **SKF-82958**. A large dose (100 .mu.g/kg, i.m.) of MK-801 produced marked central nervous system depression. In combination with the dopamine agonists N-0923 and **SKF-82958**, MK-801 depressed contraversive circling in all doses studied. This study using **hemiparkinsonian** monkeys does not support the suggestion that a noncompetitive N-methyl-D-aspartate antagonist such as MK-801 would be useful in adjunctive therapy of human **Parkinson**'s disease.

IT **80751-65-1, SKF-82958**
RL: BIOL (Biological study)
(**parkinsonism** inhibitory activity of, interactions with methylaspartate antagonist MK 801 in **hemiparkinsonian** monkeys in relation to)

IT **80751-65-1, SKF-82958**
RL: BIOL (Biological study)
(**parkinsonism** inhibitory activity of, interactions with methylaspartate antagonist MK 801 in **hemiparkinsonian** monkeys in relation to)

RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



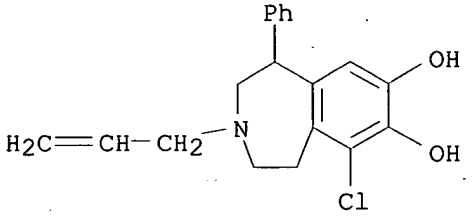
L87 ANSWER 63 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1992:543339 HCAPLUS
DN 117:143339
TI Behavioral effects of fetal substantia nigra tissue grafted into the dopamine-denervated striatum: responses to selective D1 and D2 dopamine receptor agonists
AU Becker, Jill B.; Ariano, Marjorie A.
CS Dep. Psychol., Univ. Michigan, Ann Arbor, MI, USA
SO Restorative Neurology and Neuroscience (**1991**), 3(4), 187-95
CODEN: RNNEEL; ISSN: 0922-6028
DT Journal
LA English
AB Grafts of fetal ventral mesencephalon/substantia nigra cell suspensions into the dopamine-denervated striatum have been shown to reduce many of the behavioral alterations assocd. with striatal dopamine depletion. In this report, the behavioral response to amphetamine, apomorphine, the D1 receptor agonist **SKF82958**, and the D2 receptor agonist LY171555 were tested before and after intrastriatal grafts of fetal substantia nigra, of fetal striatum or no implantation procedure in animals with unilateral dopamine denervation. Grafts of fetal substantia nigra tissue were assocd. with significant behavioral recovery, as indicated by decreased turning induced by amphetamine (P .ltoreq. 0.005), **SKF82958** ($P < 0.005$), and LY171555 ($P < 0.002$). These effects were significantly different from the response in animals that did not received grafts ($P < 0.05$) and occurred in the absence of decreased apomorphine-induced turning. These data suggest that the response to selective D1 or D2 dopamine receptor agonists is diminished following

grafts of fetal dopaminergic tissue and that this behavioral effect is dissociable from the phenomena of behavioral supersensitivity to apomorphine. In a subset of substantia nigra grafted animals, it was found that D1 or D2 dopamine receptor antagonists administered 30 min prior to apomorphine could significantly reduce apomorphine-induced turning.

IT **80751-65-1, SKF82958**
RL: BIOL (Biological study)
(behavioral effects of fetal substantia nigra tissue grafted into dopamine-denervated striatum response to)

IT **80751-65-1, SKF82958**
RL: BIOL (Biological study)
(behavioral effects of fetal substantia nigra tissue grafted into dopamine-denervated striatum response to)

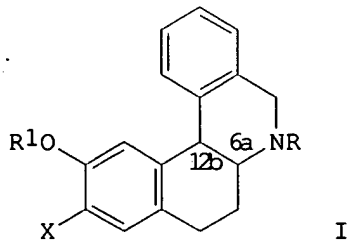
RN 80751-65-1 HCAPLUS
CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)- (9CI) (CA INDEX NAME)



L87 ANSWER 64 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1991:656024 HCAPLUS
DN 115:256024
TI Preparation of hexahydrobenzo[a]phenanthridines as dopamine receptor ligands
IN **Nichols, David E.**
PA Purdue Research Foundation, USA
SO U.S., 6 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 5047536	A	19910910	US 1989-325140	19890317 <--
PRAI US 1989-325140		19890317 <--		

OS MARPAT 115:256024
GI



I

AB The title compds. (I; R = H, alkyl; R1 = H, Bz, Me3CCO; X = H, Cl, Br,

iodo, OR2, R2 = H, Bz, Me3CCO; R1R2 = CH2; H atoms at 6a and 12b positions are trans) were prepd. as dopamine receptor ligands (no data). Thus, 6,7-dimethoxy-.beta.-tetralone was condensed with PhCH2NH2 and the enamine product N-benzoylated to give, after photolysis and borane redn., trans-I (R = CH2Ph, R1 - Me, X = OMe).HCl which was converted in 2 steps to trans-I (R = R1 = H, X = OH).HCl.

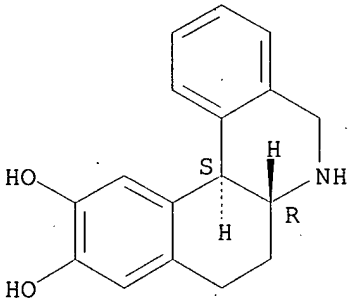
IT **137417-08-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as dopamine receptor ligand)

IT **137417-08-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as dopamine receptor ligand)

RN 137417-08-4 HCAPLUS

CN Benzo[a]phenanthridine-10,11-diol, 5,6,6a,7,8,12b-hexahydro-, hydrochloride, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



● HCl

L87 ANSWER 65 OF 66 HCAPLUS COPYRIGHT 2003 ACS

AN 1991:485324 HCAPLUS

DN 115:85324

TI **Dihydrexidine**, a full dopamine D1 agonist, reduces MPTP-induced **parkinsonism** in monkeys

AU Taylor, Jane R.; Lawrence, Matthew S.; Redmond, D. Eugene, Jr.; Elsworth, John D.; Roth, Robert H.; **Nichols, David E.**; **Mailman, Richard B.**

CS Sch. Med., Yale Univ., New Haven, CT, 06510, USA

SO European Journal of Pharmacology (**1991**), 199(3), 389-91
CODEN: EJPHAZ; ISSN: 0014-2999

DT Journal

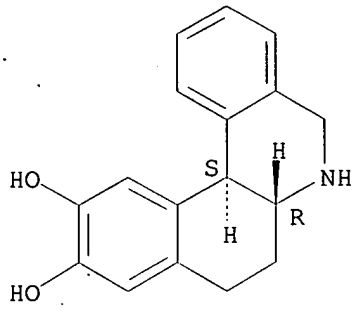
LA English

AB **Dihydrexidine** was tested in non-human primates pretreated with the dopaminergic neurotoxicant MPTP, which results in a **parkinsonian** syndrome in humans and non-human primates. These data show that **dihydrexidine** dramatically attenuated **parkinsonian** signs, including tremor, motor freezing, abnormal posture, rigidity, and bradykinesia, while increasing eye blink rates in MPTP-treated monkeys. Thus, contrary to accepted views, these results suggest a crit. role for D1 receptor occupancy in attenuation of **parkinsonian** signs. These data do demonstrate that striking improvements in **parkinsonism** can result from drugs with activity at D1-like receptors.

IT **123039-93-0, Dihydrexidine**
RL: BIOL (Biological study)
(MPTP-induced **parkinsonism** prevention by, in monkeys)

IT **123039-93-0, Dihydrexidine**
RL: BIOL (Biological study)
(MPTP-induced **parkinsonism** prevention by, in monkeys)
RN 123039-93-0 HCAPLUS
CN Benzo[a]phenanthridine-10,11-diol, 5,6,6a,7,8,12b-hexahydro-, (6aR,12bS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L87 ANSWER 66 OF 66 HCAPLUS COPYRIGHT 2003 ACS
AN 1980:446455 HCAPLUS
DN 93:46455
TI 6-Halo-3-lower alkyl-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepines
IN Weinstock, Joseph
PA Smithkline Corp., USA
SO U.S., 7 pp. Cont.-in-part of U.S. No. 4,160,765.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 8

	PATENT NO.	KIND	DATE		APPLICATION NO.	DATE	
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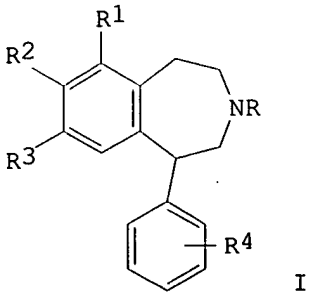
	US 4160765	A	19790710		US 1976-742965	19761117	<--
	ZA 7705910	A	19780530		ZA 1977-5910	19771004	<--
PRAI	US 1976-742965		19761117	<--			
	ZA 1977-5910		19771004	<--			

GI



I

AB N-(2-Hydroxy-2-phenylethyl)phenethylamines were heated with CF3CO2H and H2SO4 to give the title compds. I (R = Me, Et, allyl; R1 = halo, CF3; R2 and R3 are OH, alkanoyloxy; R4 = H, Me, halo, OMe, CF3), which exhibited anti-**Parkinsonism** activity. Thus, 2,3,4-Cl(MeO)2C6H2CH2CH2NH2

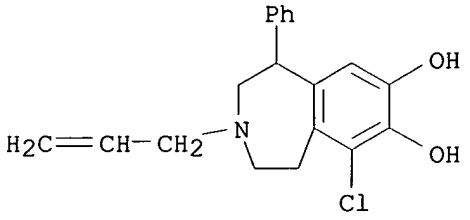
reacted with styrene oxide to give 2,3,4-Cl(MeO)2C6H2CH2CH2NHCH2CH(OH)Ph (II), a mixt. of II, CF3CO2H, and H2SO4 was refluxed to yield I (R = R4 = H, R1 = Cl, R2 = R3 = OMe), and the product was N-methylated and O-demethylated to give I (R = Me, R1 = Cl, R2 = R3 = OH, R4 = H).

IT **74115-01-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and anti-**Parkinsonism** activity of)

IT **74115-01-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and anti-**Parkinsonism** activity of)

RN 74115-01-8 HCAPLUS

CN 1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-3-(2-propenyl)-, hydrobromide (9CI) (CA INDEX NAME)



● HBr

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 s dinapsoline/cn
L1             1 DINAPSOLINE/CN

=> d l1

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS
RN   221032-27-5  REGISTRY
CN   1H-Dibenz[de,h]isoquinoline-8,9-diol, 2,3,7,11b-tetrahydro- (9CI)  (CA
     INDEX NAME)
OTHER NAMES:
CN   Dinapsoline
FS   3D CONCORD
MF   C16 H15 N O2
CI   COM
SR   CA
LC   STN Files:   BIOSIS, CA, CAPLUS, TOXCENTER, USPATFULL
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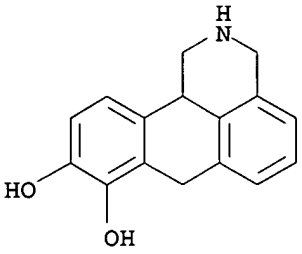


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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

               6 REFERENCES IN FILE CA (1962 TO DATE)
               2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
               6 REFERENCES IN FILE CAPLUS (1962 TO DATE)


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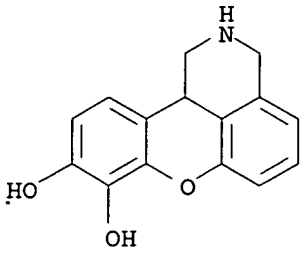
L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 313484-61-6 REGISTRY
CN [1]Benzopyrano[4,3,2-de]isoquinoline-8,9-diol, 1,2,3,11b-tetrahydro-, hydrobromide (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Dinoxyline**
MF C15 H13 N O3 . Br H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



● HBr

3 REFERENCES IN FILE CA (1962 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
3 REFERENCES IN FILE CAPLUS (1962 TO DATE)

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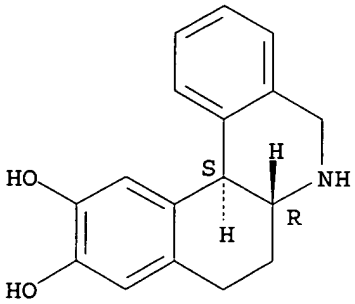
L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 123039-93-0 REGISTRY
CN Benzo[a]phenanthridine-10,11-diol, 5,6,6a,7,8,12b-hexahydro-, (6aR,12bS)-rel- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Benzo[a]phenanthridine-10,11-diol, 5,6,6a,7,8,12b-hexahydro-, trans-
OTHER NAMES:
CN **Dihydrexidine**
FS STEREOSEARCH
DR 126295-91-8
MF C17 H17 N O2
CI COM
SR CA
LC STN Files: ADISINSIGHT, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CIN, CSCHEM, DRUGNL, DRUGUPDATES, EMBASE, MEDLINE, PHAR, PROMT, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

56 REFERENCES IN FILE CA (1962 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
56 REFERENCES IN FILE CAPLUS (1962 TO DATE)